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XANTHOMA OF THE SKIN AND LARYNX

ASSOCIATED WITH CARCINOMA OF THE STOMACH AND A REGRESSIVE XANTHOMA OF THE PONS

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PHILADELPHIA

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REPORT OF A CASE

NON-NEOPLASTIC NATURE OF XANTHOMA IN THE CASE REPORTED

It is by now the consensus, although knowledge of the fact has not yet become sufficiently disseminated among members of the medical

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profession, that the xanthomatous process has, fundamentally, nothing to do with neoplasia. The suffix "oma" was unfortunately chosen, at a time when the nature of the yellow nodules of the skin had been insufficiently investigated, and, in the absence of any established cause for their development, these nodules were hastily classified as tumors. Perhaps an exception to the foregoing statement may be made in the case of the exceptionally rare xanthosarcomas, but even in regard to these neoplasms there is an extreme likelihood that fundamentally the lesions are nothing more than fibromas or fibrosarcomas which have secondarily undergone a xanthomatous metamorphosis. Be this as it may, it seems thoroughly established by now that the yellow, xanthomatous phases of xanthomatous lesions are referable to infiltration of cells by fatty substances "absorbed" from surrounding lymph surcharged with lipid —a process entirely different from neoplasia.

In reporting, then, the case of a patient exhibiting a carcinoma of the stomach and a regressing xanthoma of the pons, we wish to state at the outset that we have no intention of correlating the cells of the xanthoma with those of the neoplasm. Whatever connection may exist between the two must be through the agency of some intermediary process, the lipids (which, it is true, are associated both with cancer and with xanthoma) being the most inviting because they are the most tangible. Our experience is all the more in order because Weidman and Boston [1] are about to publish a report of another case of xanthoma tuberosum in which there was an adenocarcinoma at the duodenal papilla.

The involvement of the larynx is excessively rare; it is interesting to note that another abnormality ascribed to the lipids, namely colloid degeneration of the larynx, was recently reported by Kreibich.[2] As he found a disturbance of the lipids in the skin of his patients (two diabetic or subdiabetic sisters), one more phase in general systemic fatty disturbances is introduced, i. e., the effect of such a disturbance on the larynx.

There is a message, too, to dermatologists because the case under consideration had been previously reported as one of erythema telangiectodes and parapsoriasis besides the xanthoma (Greenbaum [3]), and any light in the way of internal pathologic changes proves valuable in adding to an understanding of the mechanism of these two dermatoses of unknown etiology.

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1. Weidman, F. D., and Boston, L. N.: Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scars of an Intercurrent Zoster: Adenocarcinoma of the Ampulla of Vater at Necropsy, Arch. Int. Med. **59**:793 (May) 1937.

2. Kreibich, C.: Zosteriform Xanthoma, Arch. f. Dermat. u. Syph. **152**:365 (Dec. 3) 1926.

3. Greenbaum, S. S.: Xanthoma with Erythema Telangiectodes and Parapsoriasis, Arch. Dermat. & Syph. **13**:78 (Jan.) 1926.

CLINICAL DATA

History.—Details of the earlier stages are given in Greenbaum's article.[8] The patient, A. P., was a Jewish man, aged 25. The disease appeared first in 1918 as a mottled reddening of the face, referred by the patient to exposure incident to his occupation. A few months later yellowish nodules developed on the edges of the eyelids. Up to 1926, other nodules appeared on the chin and adjacent to the nose, in the groins and around the anus. There were a few on the trunk and upper extremities. There were no subjective symptoms.

Greenbaum stated that while the patient was not poorly nourished in the sense of undernourishment due to a lack of food, he appeared undernourished as a result of malassimilation and there was an odor of the breath resembling that of apple cider (acidosis?). Greenbaum described the dermatologic phases with extreme accuracy; among other things he indicated that even when the erythema was removed by pressure with the diascope an underlying yellowish tint remained. This was considered as clear evidence that at that time xanthomatous infiltration had occurred in the erythematous areas as well as in the nodules.

Laboratory tests at that time indicated absence of hyperglycemia or hypercholesteremia; three tests were made for the latter. All the urinary examinations gave normal results; in one instance the specific gravity was as low as 1.002. Pentose was not found. The Kolmer and Kahn tests for syphilis were negative.

The therapy at that time is recorded on account of the bearing it may have had on subsequent findings. The patient was placed on the cholesterol-free diet of Chauffard, and 15 minims (0.9 cc.) of oil of turpentine was administered daily. The larger xanthomatous nodules were excised, and the smaller ones were destroyed by galvanocauterization. The erythema was treated with roentgen rays and later by multiple ignipuncture. These last observations are in order in view of the keloidal aspects of all the lesions; however, it should be emphasized that the illustrations in Greenbaum's article show the keloidal conformation prior to the aforementioned treatment. Were it not for this fact, the treatment might be held accountable for the keloidal expressions present when the patient came under our observation.

For histologic studies nodules from the face and plaques from the trunk, as well as a nodule from the angle of the mouth, were employed. There was marked hyperplasia of the connective tissue, intermixed with characteristic foam cells and numerous multinucleated cells. In frozen sections, stained with scarlet red and hematoxylin, there was a "massed deposition of a lipoidal substance."

Greenbaum made a diagnosis of parapsoriasis, and histologic sections were sent to Pollitzer, who originated the term parapsoriasis; he reported that he was inclined to agree with that diagnosis. The particular type of lesion to which Greenbaum referred was *érythrodermie pityriasique en plaques disséminées.* Greenbaum recorded that the lipoid accumulations were less marked in the region of erythema than in the fibrous parts, and he pointed to the theory that the hyperplasia of fibrous tissue precedes, rather than follows, the lipoid infiltration.

In 1919 the patient came under the observation of Dr. Jay Frank Schamberg at the Graduate Hospital of the University of Pennsylvania, where a tonsillectomy was performed. A plastic operation was also performed on the eyelids on account of the xanthomatous nodules. In view of the hoarseness, Dr. Chevalier Jackson performed a direct bronchoscopy; he reported that there was an infiltration of the larynx, probably xanthomatous. Material was excised, and microscopic examinations showed the presence of xanthoma. Examinations of the blood at that

time gave normal figures for the red cells (4,650,000 and 4,310,000). The number of leukocytes was slightly increased (9,750 and 11,150). The hemoglobin content was 68 and 65 per cent. The differential count gave normal values. The Wassermann reaction of the blood was again negative.

The direct van den Bergh test was negative but the indirect test yielded 0.1 mg. of bilirubin. Urobilinogen was present in specimens of urine diluted 1:20 and 1:30. These tests were repeated and the values confirmed. In three tests the cholesterol in the blood was 265, 240 and 200 mg., respectively, per hundred

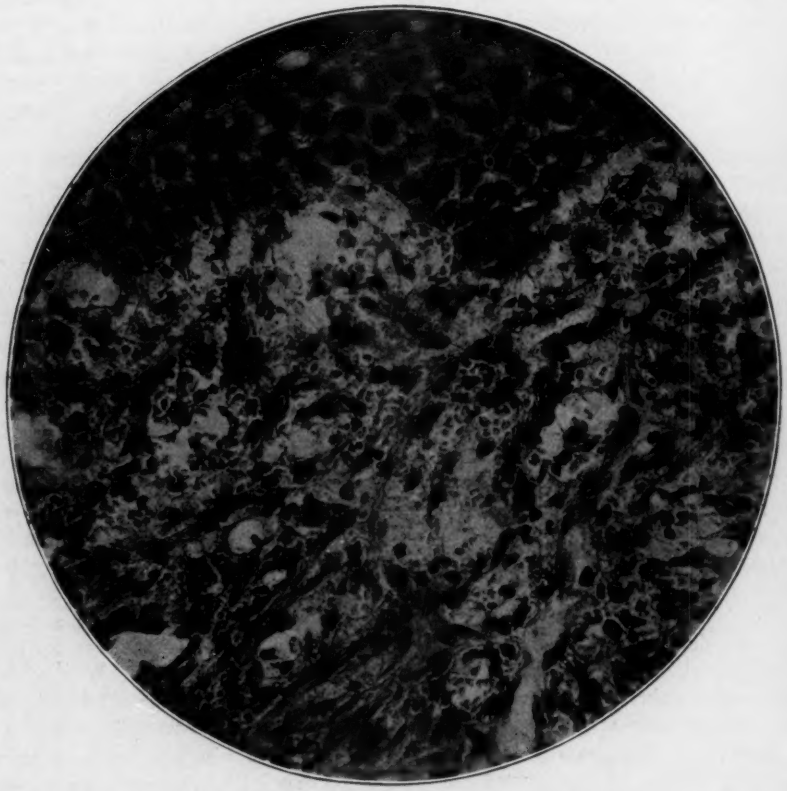

Fig. 1.—Photomicrograph of a biopsy (bronchoscopic) specimen from the larynx showing an area of capillary engorgement and hemorrhage.

cubic centimeters at intervals of from three to ten days. The values for the other substances per hundred cubic centimeters of blood were as follows: calcium, 10.6 mg.; sugar, 107 and 98 mg.; urea nitrogen, 10 mg.; uric acid, 3 mg., and chlorides, 498 mg. The value for the carbon dioxide was 57 volumes per cent. The icterus index was 8; the plasma phosphorus (inorganic), 3.4 mg. per hundred cubic centimeters of blood. In the sugar tolerance test the sugar in the blood rose to 286 mg. per hundred cubic centimeters and 2.38 Gm. appeared in the urine. On the basis of these observations the patient was given foods rich in cholesterol; he also received insulin and as much as 15 Gm. of cholesterol daily over a short period.

Course in the Philadelphia General Hospital.—On admission to our observation at the Philadelphia General Hospital on Dec. 12, 1929, the patient showed extreme emaciation, weakness and grave anemia. The xanthomatous lesions had the distribution originally described by Greenbaum. However, the erythema did not impress us as being associated with infiltration as in the parapsoriasis originally noted. The scars of the ophthalmologic operations were visible; xanthomas had not developed in them. The patient was markedly hoarse. There was no jaundice or edema. There was a definite inflammatory areola around the xanthomatous lesions, suggesting that they were diabetic. The left arm exhibited several

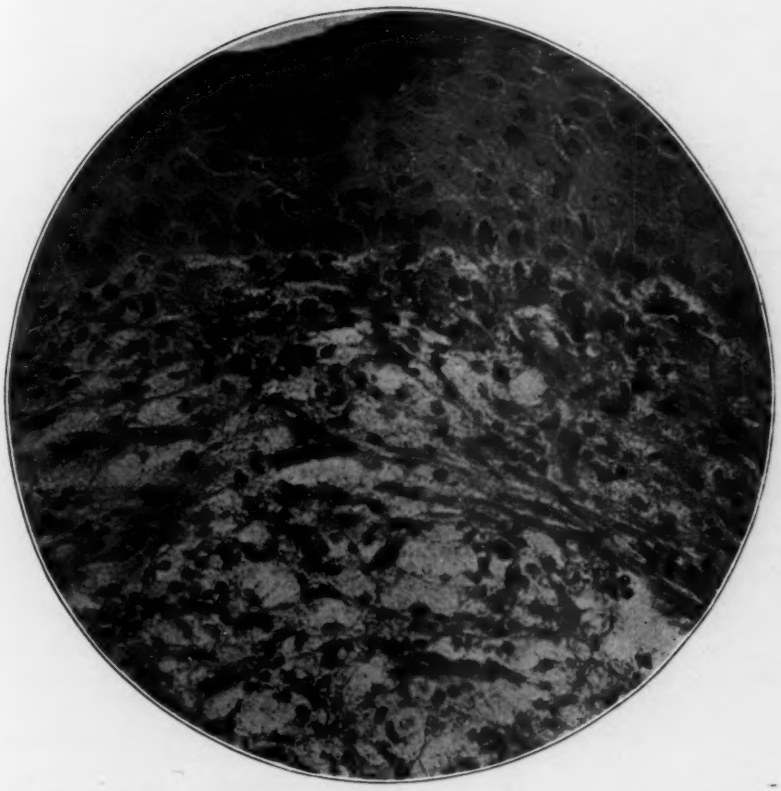

Fig. 2.—Photomicrograph of a biopsy (bronchoscopic) specimen from the larynx. Numerous more or less coalescent xanthoma cells are shown in the lower part of the illustration.

keloidal, erythematous areas at the sites from which skin used in the skin graft of the eyelids had been removed. There were no xanthomatous lesions in these scars. The epiglottis seemed to be reddened, and there was slight thickening of the vocal cords.

All the reflexes were exaggerated, but there were no special abnormal neurologic reactions.

Small amounts of carotene were injected into one of the xanthomatous lesions, but they did not produce the effect tested for, i. e., an intensification of the yellow

color already present. Probably sufficiently large quantities were not employed.

The urine was normal in all respects; both albumin and sugar were absent. The renal function, however, was impaired; the elimination of phenolsulfonphthalein was 30 per cent in the first and 5 per cent in the second hour.

The blood count was as follows: hemoglobin, from 8.1 to 8.4 Gm. per hundred cubic centimeters; red cells, from 2,640,000 to 3,490,000; white cells, from 4,700 to 9,900. The differential count was normal on each examination.

The Wassermann reaction of the blood was negative. The urea nitrogen content was 10 mg. per hundred cubic centimeters; the sugar content (not fasting), from 87 to 100 mg.; the cholesterol content, from 160 to 170 mg.

Roentgenologic examination revealed no demonstrable lesions of the lungs, liver, spleen or skull, no signs of intracranial pressure and no convolutional atrophy. The sella turcica was normal.

During the patient's stay in the hospital the temperature was normal; the pulse rate varied from 76 to 90, and the respiratory rate, from 20 to 25. He complained only of weakness, which was evidently general and the result of his secondary, progressive anemia.

The cutaneous condition progressed slowly, new lesions forming and older ones coalescing. Dysphagia developed; this was attributed to the development of further xanthomatous changes in the larynx.

The neurologic examination focused attention on the spinal cord. There was an internal squint of the right eye, but except for this there appeared to be no palsies of the cranial nerves. There were marked symptoms of involvement of the pyramidal tracts with an increase of all the reflexes, bilateral patellar and ankle clonus and a Hoffmann and a Babinski sign. The sense of position was definitely impaired in both lower extremities; it was normal in the upper extremities. The sense of vibration was normal over all the bony prominences in all four extremities. There was slight atonia in the finger-to-nose test on both sides. The diagnosis was "posterolateral sclerosis of the anemic type."

The weakness became progressive until hypostatic pneumonia intervened. There seemed to be no resistance to this, as there was no leukocytosis or hyperpyrexia. The patient died afebrile.

CLINICAL SUMMARY

When we first saw the patient the outstanding symptom was the profound secondary anemia of progressive, pernicious type; we believed that it was consequent on impediment to swallowing, probably from the presence of xanthomatous masses at least near the trachea and probably elsewhere. The neurologic symptoms were ascribed to the posterolateral sclerosis frequently observed in extreme anemia. The inflammatory areola around the xanthomatous nodules recalled the diabetic form of xanthoma, and it was this observation which prompted the roentgenologic examination of the base of the skull. The confirmation of the diabetic state was only partial (dextrose tolerance test). That Greenbaum had suspected the presence of a diabetic condition is shown by the fact that he also made a test for pentose; that substance was absent. We believed that there might be a disturbance of the carbohydrate metabolism which was not expressed by a chemically demonstrable substance, as Bickel and Kauffmann-Cosla [4] stated that they could identify otherwise unrecognizable disturbance of the carbohydrate metabolism by noting upsets of the normal ratio of carbon to nitrogen in the urine. Several

4. Bickel, A., and Kauffmann-Cosla, O.: Zur pathologischen Physiologie und Klinik der dysoxydativen Carbonurie, Virchows Arch. f. path. Anat. **259**:186, 1926.

competent internists, called in consultation, did not recognize a mass in the stomach.

The fact that the values for cholesterol were persistently normal in the earlier stages but increased over a period of at least ten days in a later stage is puzzling. All the determinations were made by the same chemist, although the patient was in two different hospitals. There appears to be no alternative than to understand that in this patient hypercholesteremia was present at one period and absent at others.

Fig. 3.—The head and neck at necropsy. The lesions were more brown (residual pigmentation) than yellow.

MACROSCOPIC OBSERVATIONS AT NECROPSY

The body was profoundly emaciated, weighing only 75 pounds (34 Kg.). The internal body cavities revealed nothing noteworthy except some small, firm lobular masses on the peritoneal lining. There was 100 cc. of clear fluid in the pericardial sac. All the tissues were profoundly anemic; only a small amount of blood escaped from the ends of severed vessels, and very little was present in the cardiac chambers or great vessels nearby. Sufficient quantities could not be collected for satisfactory chemical analysis. All the viscera likewise showed the gravely anemic appearances observed clinically. In general all the organs were small, pale and yellowish.

Larynx.—No masses were found in the tissues around the larynx or esophagus to substantiate the clinical impression that the difficulty in swallowing was due to the presence of xanthomatous tumors in that region. A hard, yellowish swelling was observed back of the pharynx; on incision, however, this proved to be a degenerated tendon. No xanthomatous nodules could be discerned in the epiglottis. It was diffusely thickened and somewhat reddened. While there was some distortion of the epiglottis as a result of fibrous thickening, there were no spectacular deformities; certainly there were no ulcerations or definite neoplastic formations.

Lungs.—The lungs were intensely edematous; on pressure great quantities of watery fluid welled from the parenchyma. Globules of fat were intermixed in sufficient number to impart a milky or even definitely oily quality to the fluid.

Fig. 4.—The anus and perineum at necropsy. Owing to regressive changes the color was by this time more brown than yellow (residual pigment). The cicatricial effect above the anus accounts for its dilatation.

There was a rather extensive region of bronchopneumonic consolidation of the left lung.

Fat in Pulmonary Fluid: Approximately 20 cc. of the fluid was shaken with sudan III and centrifugated. It was estimated by the naked eye that 25 per cent was neutral fat (fig. 5). The cholesterol content of this fluid was 45 mg. per hundred cubic centimeters.[5] Presumably the fat was mostly neutral fat.

Heart.—There were no abnormalities except the degenerative changes incident to the severe anemia.

Liver.—The liver was small, weighed 850 Gm. and, like the other organs, was yellow and showed evidences of degeneration. Yet there was a firm consistency suggesting that there might be a certain proportion of fibrous tissue intermixed.

5. This approximates the normal figure for body fluids in general.

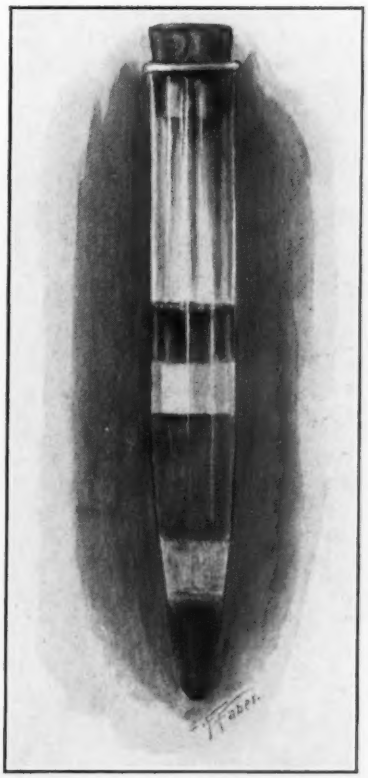

Fig. 5.—Edematous fluid obtained from the lungs at necropsy stained with sudan III and centrifugated. The upper stratum represents fat; the second, an emulsion of fat and serum; the third, serum and cell detritus; the fourth, cells and globules of fat (in three differently colored layers).

The cut surface presented the typical nutmeg appearance of passive congestion. There were not more than a dozen metastatic carcinomatous lesions over the surface of the liver; these lesions ranged to a maximum of from 6 to 8 mm. in diameter.

Stomach.—There was a mass in the pylorus measuring approximately 10 cm. in length; the regional lymph nodes were large, hard and adherent to the surrounding tissue.

Kidneys.—The kidneys were small, weighing 100 Gm. and measuring 9 by 6 by 3 cm. They were definitely firmer than normal. It appeared, too, that the cortex was decreased out of proportion to the medulla.

Spleen.—The organ was small and bluish red, but the surface was smooth. On the cut surface the trabeculae were definitely more prominent than is normal.

Bladder.—The bladder appeared normal except for pseudomelanotic pigmentation at the fundus.

Prostate.—The gland appeared normal.

Brain.—The only grossly recognizable abnormality consisted in the "tumor" of the pons, which occupied practically the entire extent of this structure. Only a narrow rim of normal-appearing tissue, measuring 2 or 3 mm. in width, remained around the tumor. The latter projected slightly above the cut surface; it was translucent and grayish white but showed a number of small, irregular, more opaque areas. Hemorrhages were not recognized, nor any yellow pigmentation.

Spinal Cord.—An indefinitely outlined nodule, 5 mm. in diameter, was found on the right side of the cervical portion of the cord in the lateral pyramidal tract. It had the same general characteristics as the lesion in the pons.

HISTOPATHOLOGIC DATA

Lung.—The alveoli were fully expanded. Their walls were thin. They were largely occupied by desquamated and vacuolated alveolar epithelium; there were no leukocytes. The epithelium was swollen to two or three times its normal size and had a highly rarefied appearance by reason of the large vacuoles crowding it; staining with sudan III did not demonstrate fat. The nuclei were deformed, pyknotic or scarcely recognizable. There was no fibrin in the air sacs. In some blocks of tissue there were but small quantities of the pink granular material which was to be expected from the extremely edematous state observed at necropsy, but in others it was present in large quantity. The lining epithelium of the bronchi was largely absent; what remained was largely desquamated. The lumens contained small numbers of vacuolated cells similar to those seen in the alveoli.

Epiglottis.—Ulceration was not observed, although the epithelium was definitely thinned immediately over the summit of the epiglottis and was absent at one place; its thinnest part consisted of but four or five layers of highly condensed, shrunken cells. The major pathologic changes occurred immediately under this position and consisted of fibrosis and lymphoid infiltration. The former extended deeply enough to surround the mucous glands and was of the old adult type. Its spindle cells were hyperplastic and associated with moderately increased numbers of capillaries and lymphoid cells. The round cell infiltrate consisted exclusively of lymphocytic and plasma cells; it predominated at the level immediately under the epithelium. While some such areas could be regarded as a normal lymphadenoid expression, there still remained in addition a diffuse infiltration which

was certainly not in that category. A few giant cells of the foreign body type were located in some of the focal accumulations.

Xanthoma cells could not be demonstrated, even in sections stained with sudan III. In these sections, however, accumulations of fat were seen in some of the spindle cells of the submucosa, in the cytoplasm of mucous glands and in the fibers of nerve trunks. The largest quantities of fat were found in the dense fibrous tissue of the deeper parts, but this could be readily identified either as the large (deformed) globules of normal areolar fat or as disintegrated portions of them. The fibrosing processes within which these globules of fat were enclosed easily accounted (by pressure) for their disruption. The elastic fibers inclined to a yellow tint in the sudan III preparations; we believe that the appearance of those fibers was due not to an overstaining by the sudan III but to a fatty change.

The cartilage appeared normal save for the presence of smaller and larger discrete globules of fat (sudan III preparations) within the cartilage cells. This was regarded as an infiltration with the crushed fat of the submucosa which had been transported more or less indiscriminately to a deeper position. It was not viewed as an expression of degeneration because the globules of fat were not of the minute, comparatively uniform-sized type usually seen in fatty degeneration. The character of the nuclei could not be invoked in settling this point because the nuclei of cartilage cells are normally small, comparatively insignificant structures.[6]

Retrolaryngeal Tendon.—This structure was included for histologic examination because it was the only material close to the larynx that was yellow or was at all suggestive of xanthoma. The only abnormality found was hyperplasia and fragmentation of elastic tissue in small scattered foci; the elastic tissue appeared far too abundant for such a rigid, nonelastic structure as a tendon. In sections treated with hematoxylin and eosin this material stained more strongly pink than normal, and in sudan III preparations it took on a definitely yellow coloration. Around arteries there were particularly large masses, and the internal elastic laminae were far more robust than normal. Furthermore, there were smooth pink bands of this material under the endothelium of veins that recalled the distribution, at least, of amyloid. Xanthoma cells were not found in this section.

Aorta.—The intima was definitely thickened by fibrous tissue and stained metachromatically in sections treated with hematoxylin and eosin. Areas of vacuolation occurred throughout its entire extent. The most luminal parts of the intima were the ones most severely affected; while the vacuoles were distributed for the most part diffusely, there were foci into which they coalesced into comparatively large cavernous spaces. The vacuoles had indefinite walls and were not associated with special cellular reactions. In the case of a particularly large accumulation of such vacuoles, all the partitions appeared to have disappeared, produing an elongated cyst the lining of which was incrusted with pink granular material in which nuclei and small xanthoma cells (some pigmented) were suspended. We can understand that the latter consisted of xanthoma cells which had fused. The elastic tissue in the media was most conspicuous because its fibers were so robust and stained intense pink. Frozen sections stained with sudan III demonstrated a definite yellow tint in the elastic tissue; there was no trace of red. In the intima some of the connective tissue cells were crowded with small globules of fat.

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6. Sections of the larynx from the case of Finney and his co-workers which we were privileged to study showed similar globules of fat. The nuclei, however, were not in the least degenerate.

Liver.—The capsule appeared normal. Immediately under it was a well circumscribed area of adenocarcinomatous tissue. The central parts were degenerate or almost necrotic; in them, portions of a fibrosed interstitial substance persisted. The cancer cells concerned were large and polygonal or, at times, rounded. The cytoplasm was pink, from finely to coarsely granular and frequently vacuolated. The vacuolation was at times so extreme that the entire cell was involved, and in sites in which such cells occurred in masses whole areas took on a coarsely reticulated appearance. The nuclei of the smaller and less degenerate cells were large (even gigantic) and hyperchromatic, but those of the larger, more vacuolated

Fig. 6.—Photomicrograph of a section from the postlaryngeal tendon, showing hyperplasia and degeneration of periarterial elastic tissue. The smooth, pale tissue visible in the lower part of the illustration is normal collagenous tissue; the coarsely fibrillar zone above is solely elastic tissue.

and degenerate cells were deformed, pyknotic or flattened against the cell walls after the fashion of the seal ring cell.

Frozen sections stained with sudan III indicated that the vacuoles were not fatty; only in exceptional cases was it possible to discern minute red, powdery grains in some of the larger, more degenerate cells. When present, however, these grains were numerous enough at times to make up a large proportion of the entire cellular substance.

Individual cells at times had such polygonal outlines and such large, hyperchromatic nuclei and fibrillar cytoplasm that individually they could be mistaken

for prickle cells. However, prickle cells could not be demonstrated; furthermore, sites were eventually observed in which these cells were arranged in definite acini. Abnormal mitotic figures were plentiful. In no case could a blue color be identified in the vacuoles to bear out the impression received at necropsy that mucin might be present.

As to the hepatic tissue itself, the interstitial substance was definitely fibrosed, moderately infiltrated with lymphocytes and traversed by a few hyperplastic bile ducts. The picture was not that of a frank cirrhosis. There was no biliary pigmentation. The parenchymal cells were small and coarsely granular; those in the center of lobules were moderately infiltrated with pigment and minute globules of fat (this appearance was confirmed in sudan III preparations). The capillary sinuses contained little blood, but instead contained fairly large quantities of coarse granular or reticular pink material. The Kupffer cells did not contain excess fat.

Kidney.—The interstitial substance was severely infiltrated with lymphoid cells both in the cortex and in the medulla; fibrosis was associated. The cortical tubules were highly atrophic; many, however, were distended by granular detritus and pus. The glomerular tufts were reduced in number, apparently from fibrosis and atrophy; the remaining ones were enlarged. Bowman's capsule was fibrosed. The walls of the arteries were tremendously thickened and hyalinized.

Spleen.—There were no recognizable pathologic changes in this organ. Perhaps the number of lymphoid cells in the pulp was reduced, but there was no endothelial hyperplasia.

Adrenal Glands.—The extracapsular areolar tissue exhibited fatty atrophy; that is, the fat cells contained fairly large quantities of pink granular or fibrillar material; the nuclei were comparatively large, and the globules of fat were small and at times multiple. In the parenchyma the pars fascicularis was in general rich in lipoid substance, but in places the parts adjacent to the pars glomerulosa were comparatively poor in lipoids. The medullary cells were regarded as normal. The pars glomerulosa was also rich in lipoid substance. The impression was thus given that there had been a (minor) shift of the lipoid infiltration from the peripheral parts of the pars fascicularis into the pars glomerulosa. The globules were discrete; the cytoplasm was not of the foam cell type.

Stomach.—Several sections were examined; all exhibited an adenocarcinomatous change. In many places only the most superficial parts of the gastric mucosa were affected; in those places the cells (reflecting, perhaps, the properties of other surface coverings) tended to be polygonal and comparatively squamous, which prompted a suspicion that if metaplasia had not occurred there might have been an initial island of ectopic squamous epithelium present at the pylorus, of the order, for instance, of that which lined the esophagus. Differences in types of cells were met with in the stomach as in the metastases to the liver; degenerate or even necrotic changes were naturally more abundant and more extreme than those encountered in the liver and in the lymph nodes. There were numerous seal ring cells similar to those described for the liver, but again the sudan III preparations showed that there were no globules of fat in any of the carcinoma cells; furthermore, the vacuolar material could not be resolved into mucin. There certainly were no xanthomatous changes identifiable in these cancer cells. Infiltration of the muscular coat was not extensive but was definite enough to be in keeping with the propensities of cancer.

Mesenteric Lymph Nodes.—The normal architecture was everywhere disrupted by the neoplastic invasion. The lymph sinuses were tremendously broadened and crowded with neoplastic cells of the same general type as those already described

for other organs. The centers of some of the cancer masses exhibited early necrotic changes. Formation of acini was discoverable in a few positions, notably in the subcapsular sinuses, but even in those regions a characteristically blue mucin was not demonstrable in the seal ring cells. The latter were exhibited in greater numbers and more typically in the lymph nodes than in any other organ.

Skin.—Two portions were examined: one from one of the larger, tumor-like xanthomatous masses and a second from one of the atrophic and pigmented lesions of the axilla.

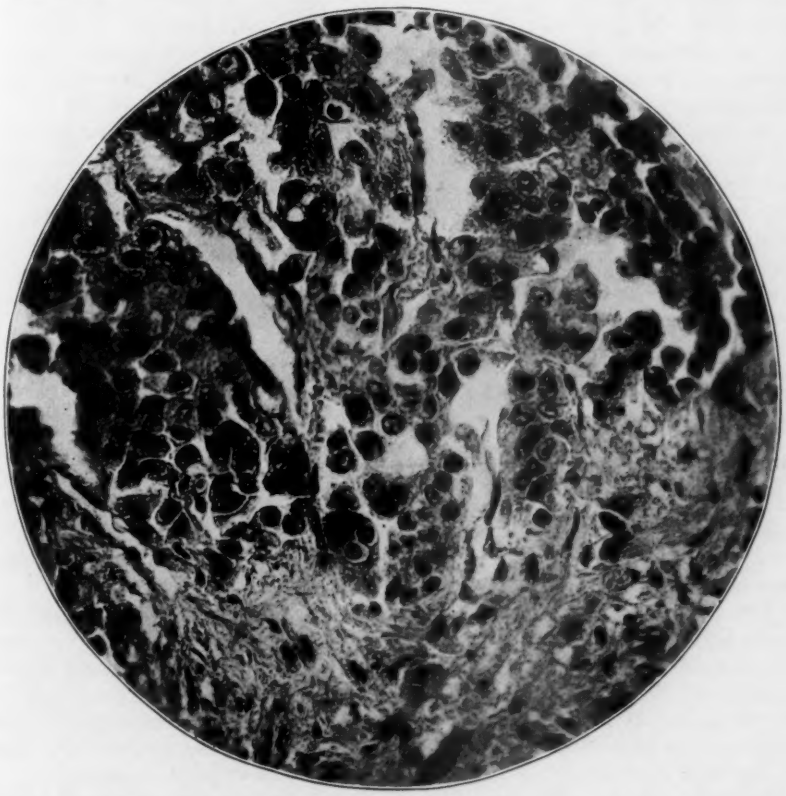

Fig. 7.—Photomicrograph of a section of the stomach wall, showing adenocarcinoma.

The Tumor-Like Lesion: Portions of the epiderm lying immediately above the xanthomatous mass exhibited moderate hyperkeratosis and acanthosis. The prickle cell layer was but slightly hyperplastic, the major epidermal changes occurring in the interpapillary pegs and inducing a moderate elongation of the pegs. The latter remained narrow for the most part and became slightly irregular in shape.

The corium was most markedly thickened, measuring at least 8 mm. The lower part consisted of fibro-elastic tissue; the upper part, almost exclusively of xanthoma cells.

The xanthomatous changes extended over large areas in which the classic features of xanthoma were exhibited, i. e., foamy polygonal cells with small round, condensed nuclei. However, dispersed through the lesion were more or less well outlined cells in which the cytoplasm was free from vacuolar or rarefactive features. Indeed, in one instance such an area was as sharply outlined as any tumor could be. The cytoplasm of these cells was coarsely granular, inclined to a metachromatic tint (sections stained with hematoxylin and eosin), and the cells were variously shaped—spheroidal, polygonal, spindle shaped or almost stellate. There was a certain approach in the form and general qualities of these cells, particularly in regard to their extremely large nuclei, to the neoplastic ones seen in the liver and elsewhere, and careful study and comparison were necessary to reach a final conclusion as to their nature. Transitions into nearby spindle cells, however, finally settled the question and showed that they were derivations from fibrous tissue.

Puzzling changes were also met at one end of the section, where young hyperplastic fibrous tissue cells were found. These were so closely placed, had such prominent nuclei and were arranged into such whorls that they closely simulated fibrosarcoma. This appearance was particularly pertinent in view of the observations in the pons. The transition of some of these spindle cells into obvious xanthoma forms was helpful in arriving at the conclusion that the xanthoma cells arose from spindle cells and not exclusively from reticulo-endothelial cells as is contended by some authors.

Pigment was encountered rather frequently, but it occurred only in comparatively small and localized areas; it was finely granular, bronze-brown and both intercellular and intracellular. Giant cells contained the pigment as well as the mononuclear xanthoma cells.

Frozen sections stained with sudan III disclosed that some of the fat in the xanthoma cells was crystalline and took the dye deeply. In addition, the spindle cells of the collagen bundles throughout the entire section contained smaller and larger quantities of minute globules of fat which were unrecognizable in the preparations treated with hematoxylin and eosin. The basal cells of the epiderm were comparatively free from fat.

The fat, as it occurred in the denser xanthomatous aggregations, appeared as coarse plates (probably crystals); these, nevertheless, still assumed a deep orange-red color when stained with sudan III. On careful analysis, however, such masses could be resolved into short, stocky anisotropic crystals. Indeed, practically all the fat in the section was of this kind. Teasings from a xanthomatous nodule which had not been frozen or stained likewise revealed but few globules of neutral fat, no cholesterol plates, and mostly short, stocky amisotropic crystals.

Sebaceous glands were not recognized. In the sweat glands nothing abnormal could be discerned except a moderate grade of atrophy; there was definite fibrosis around these glands.

Atrophic Skin from the Axilla: The changes in the epiderm were minor ones, consisting of moderate acanthosis with incidental elongation of the interpapillary pegs. In the corium xanthoma cells were scarcely recognizable; indeed, it was necessary to resort to frozen sections and to discover the anisotropic crystals with the crossed Nicol prisms before it could be concluded that the widely scattered broad, vacuolated cells were really xanthomatous and not examples of hydrops cellulae. The major pathologic change lay comparatively deep, beginning immediately above the sweat glands and extending upward into the subpapillary region. Essentially it was an old fibrotic process, exhibiting gradations from bundles of an old type to plumper spindle forms. A few giant cells of foreign body type were

likewise observed occasionally. The appearances were compatible with the concept that xanthoma cells had at one time been present but that the fatty phases had disappeared. As compared to the previously described more bulky lesion, this regressive lesion showed the same order of changes and the same kind of cells, but in different proportions. Foam cells were scarce; the large foci of transitional cells were fewer, while spindle cell fibrous tissue predominated.

Sebaceous glands were not included in the section, but sweat glands were abundant and highly developed. Moderate numbers of fat cells remained in the subcutaneous parts, but they were deformed and minute.

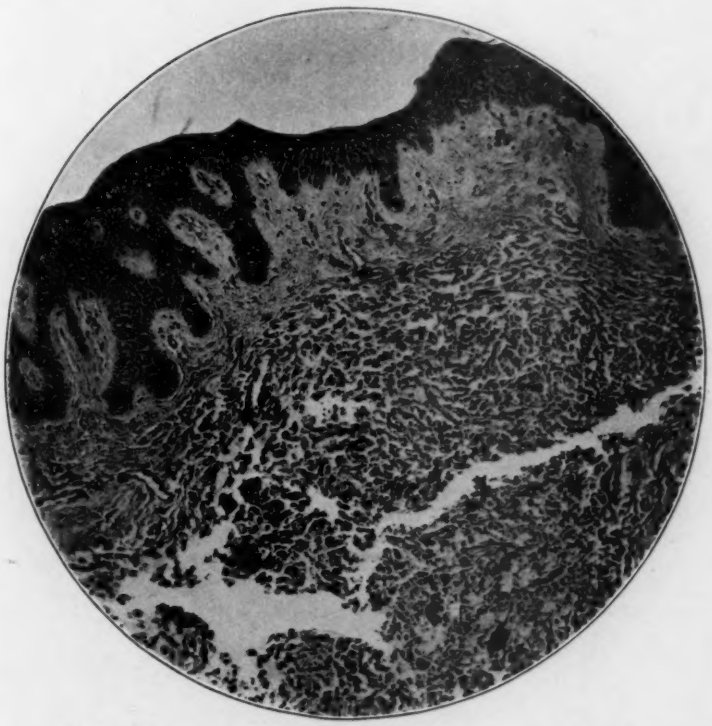

Fig. 8.—Photomicrograph of a section from a regressive lesion in the axilla. Most of the cells are spindle shaped and stellate; only a few xanthoma cells appear at the bottom of the nodule.

Pons.—In sections stained with hematoxylin and eosin a fairly well circumscribed granuloma, 20 mm. in diameter, could be identified in the anterior portion of the pons. It consisted of more or less coalescent miliary granulomas or infiltrations. The amount of nerve tissue remaining as a stroma varied from place to place; in some areas it was entirely replaced by deformed spindle, lymphoid and plasma cells. Hyperplastic capillaries were richly intermixed in such areas; in all cases they were invested by special concentrations of round cells. At times such cells were particularly closely packed and comprised a sheath far surpassing the diameter of the vessel itself. Not infrequently large polygonal cells appeared within dense lymphoid accumulations, in which case the suggestion of a specific

granuloma was indeed close. In other instances the large polygonal cells occurred in groups unassociated with lymphoid cells, both in relation to blood vessels and independently of them. The ganglion cells were degenerate.

The particularly disturbing problem in these lesions was the identity of the spindle and polygonal cells. The nucleus was almost invariably deformed in such a way as to imitate that of an endothelioid cell. The fact, however, that the polygonal cells were also observed in the regressive xanthomatous lesions of the skin and that the spindle cells frequently occurred in a broad, diffuse distribution finally influenced the decision that they were degenerated fibroblasts and not endothelioid cells.

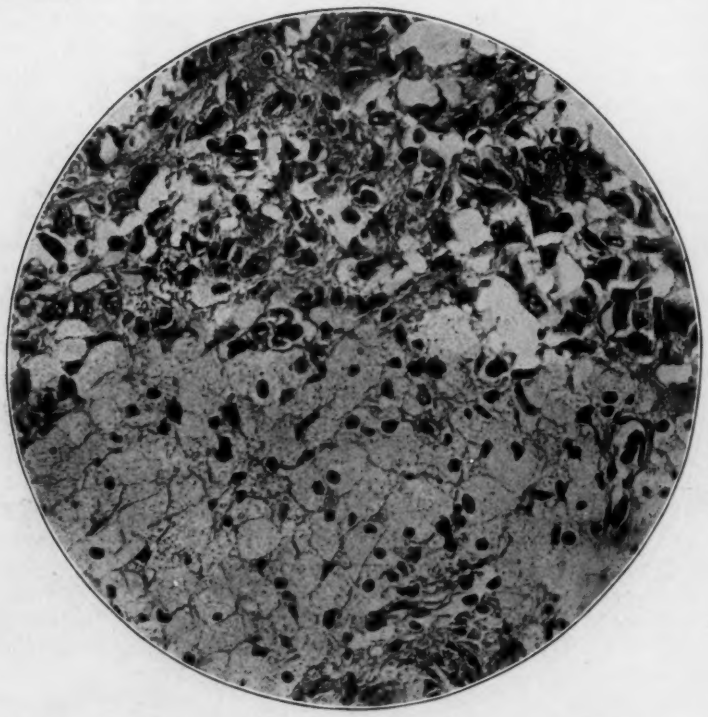

Fig. 9.—Photomicrograph of a section from a regressive lesion (proved clinically) in the axilla. The section shows a transition from xanthoma cells into stellate or spindle-shaped ones.

Frozen sections showed that these cells frequently contained globules of fat; however, in the presence of degenerate nerve tissue, the fat could represent equally well a local phagocytic process as a xanthomatous one due to hypercholesteremia.

Van Gieson, Pappenheim and Klinefield preparations assisted in differentiating the abnormal tissue from the nerve stroma but did not bring out any additional features.

Spinal Cord.—In sections stained by the Marchi method a similarly well circumscribed granuloma, 6 mm. in diameter, was found in the right lateral pyramidal tract.

PATHOLOGIC DIAGNOSIS

The pathologic diagnosis was as follows: in the stomach, adenocarcinoma with metastases to the liver and mesenteric, prevertebral and peribronchial lymph nodes; in the pons, regressive xanthoma; in the lungs, edema and bronchopneumonia; in the kidneys, chronic diffuse nephritis; in the spleen, chronic interstitial splenitis; in the aorta, hyperplasia of the elastic tissue and atheroma; in the skin, xanthoma tuberosum, fibrosis, pigmentation and atrophy; in the liver, chronic interstitial hepatitis and chronic degeneration; in the epiglottis, chronic fibrous and infiltrative

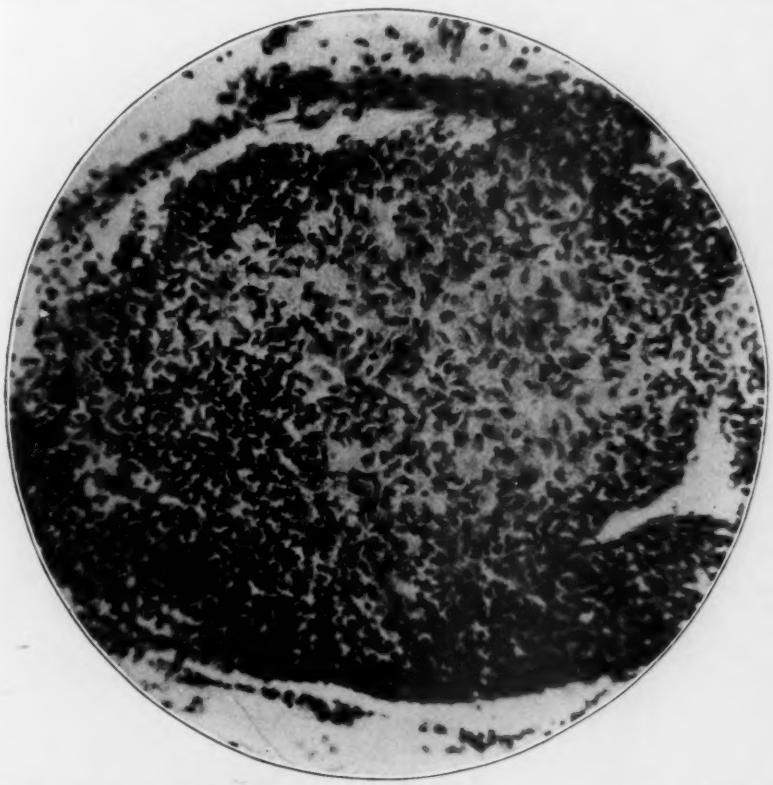

Fig. 10.—Photomicrograph of a section from the regressing xanthoma in the pons. The large cells in the center were not endothelioid. They were of the same type as the ones in regressing lesions of the skin, probably regressing xanthoma cells (compare with figure 8).

epiglottitis; in the retrolaryngeal tendon, local elastic hyperplasia with fatty degeneration.

The adrenal glands were normal.

PATHOLOGIC SUMMARY

Through the necropsy the cause of the profound anemia was explained; i. e., a fully developed gastric carcinoma with small regional metastases. The neurologic

symptoms were found to be referable (presumably) rather to a tumor in the pons than to the severe anemia. The clinical surmise that an obstruction along the esophagus accounted for the regurgitation of food was disproved; masses were not noted. The lesions in the epiglottis observed by the bronchoscopist were found to have regressed; this was in keeping with the course of the pathologic changes in the skin.

CLINICOPATHOLOGIC ANALYSIS

At this stage the entire disease complex can be resolved into several phases, i. e., the xanthoma and hypercholesteremia, the regressive

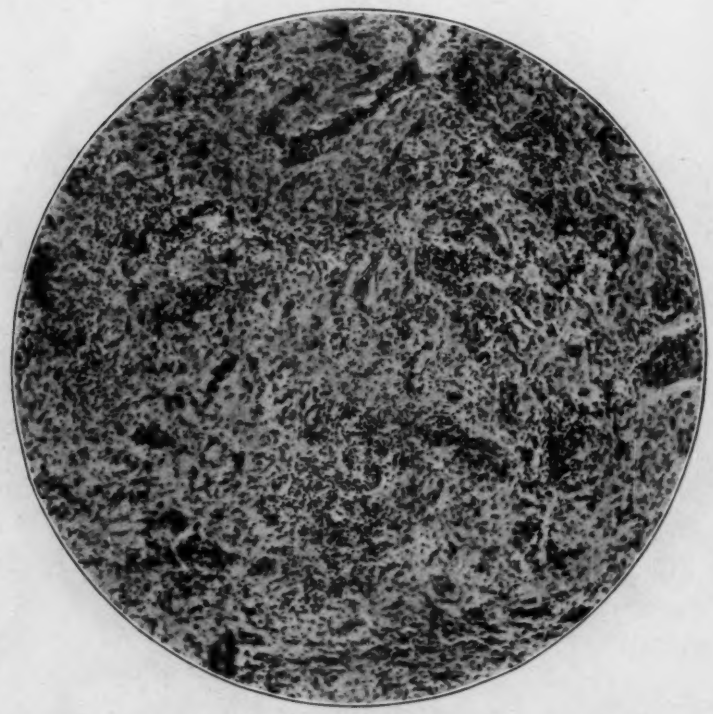

Fig. 11.—Photomicrograph of a section from the tumor of the pons (hematoxylin and eosin), showing hyperplasia of the capillaries, together with residual fibrous tissue stroma of regressive xanthomatous processes (compare with figure 7).

xanthoma of the pons, the gastric carcinoma, the grave nervous disturbances, the anemia and the erythematous (parapsoriatic) changes in the skin. The problem that now remains, and will be considered next, is to interrelate these phases, particularly in point of sequence.

The clinical history shows that the disease began in 1918 and terminated in 1930, lasting for twelve years. It is definitely known that both the erythematous and the xanthomatous changes in the skin began in 1918. It may be assumed that, even if only periodically,

hypercholesteremia was also present early in the disease; we have proof that it was present at a later period. This is orthodox, as it is already well known that hypercholesteremia can be periodic, as for instance in pregnancy, at the climacteric and in the periods of exacerbation and remission of diabetes mellitus; moreover, in Artom's [7] case also there were erythrodermic phases in addition to the xanthomatous ones.

Fig. 12.—Photomicrograph of section from a regressing xanthomatous process in the pons (Klinefield preparation demonstrating overgrowth of fibrous tissue).

As to the duration of the gastric carcinoma, it is extremely doubtful that a growth even of this size had existed for twelve years and had begun when the patient was 20 years old. On the other hand, it is altogether possible that the xanthoma in the pons began in the early days of the disease contemporaneously with the cutaneous eruption. In fact, the degenerate character of that lesion and the notoriously slow growth of xanthoma are quite in keeping with such a possibility. Fur-

7. Artom, M.: Papular Xanthoma, Gior. ital. di dermat. e sif. **68**:1060, 1927.

ther than this one cannot draw conclusions except to account for the secondary anemia after the gastric carcinoma. Rather arbitrarily and very cautiously, we should estimate the age (on morphologic grounds) of the gastric carcinoma as upward of three years. Even then, 29 years would be an early age for the development of the carcinoma, and the possibility of some special factor accounting for this precocious cancer should be considered.

The cause of the hypercholesteremia in this patient is not nearly as clear as in other patients with xanthomas whom we have observed. The fatty disease of the liver was more properly referable to the subsequently developing anemia than to any early and primarily hepatic process, i. e., one that would have to date as far back as 1918; therefore, since a pathologic condition in the liver would have been necessary to explain the xanthomas at that age, we believe that the explanation of the hypercholesteremia and xanthomas is to be found elsewhere than in the liver. Similarly, the destruction of the red blood cells (with consequent anemia) did not obtain at the period when the xanthomas first developed, and cannot be invoked to explain the development of the xanthomatous process. In view of these facts, knowledge that there is such a thing as pituitary diabetes, i. e., a disturbance of sugar metabolism, involving also fatty metabolism, in conjunction with disturbances at the base of the brain, is particularly in point. The association of acromegaly, for instance, with hyperglycemia is already well known. The decreased sugar tolerance established at one time in our patient and the diabetic type of lesion, i. e., inflammatory, have already been emphasized. However, we cannot feel altogether free to resort to the xanthoma of the pons as the explanation of the diabetes with, in turn, the hypercholesteremia and the xanthomatosis. We prefer simply to face the situation, record our reflections and leave it to the future to decide what the true order of events most likely was. With the data at hand, we consider ourselves unable to submit an orderly, logical, coherent scheme of the pathogenesis which would accommodate all of the aforementioned phases.

GENERAL CONSIDERATIONS

Besides demanding study of the case presented, the variety of clinical and morbid anatomic symptoms naturally provokes curiosity as to their relationships with body processes in general and particularly as to their relation to the manifestations in other reported cases. This justifies the succeeding sections.

THE REGRESSIVE STAGE OF XANTHOMA

It is thoroughly established clinically that xanthoma can regress; regression occurs most readily in diabetic xanthoma, in which the lesions

develop acutely and comprise less fatty and more inflammatory cellular substance. However, even diabetic xanthomas, when large and of long standing, tend to be permanent. This fact is accounted for by the notorious insolubility of cholesterol and the poor vascularization of the xanthoma nodule. In our patient it was certain that retrogression took place, particularly in the axilla, but also at numerous other places; this was proved clinically.

Histologically, however, it appears that the changes have not been recorded fully. Tissue from the axilla of our patient was valuable, therefore, because there was no doubt as to the stage of xanthoma which was pictured therein. It is true that in sections from that tissue there were a few areas in which xanthoma cells persisted in fairly large numbers and in fairly typical form. For the most part, however, the pathologic portions consisted of spindle cells the nuclei of which were so closely placed and so rich in chromatin that they at once suggested sarcoma. In addition they were gathered more or less into bundles which had a whorling arrangement. Though this arrangement resembled that of a sarcoma, it bears comparison with analogous considerations which have arisen in connection with xanthosarcomas of tendon sheaths and which were recorded by Virchow [8] in cases of corneal xanthoma many years ago.

In short, this case is an additional illustration of the accelerated, or at least disarranged, growth habits of fibrous tissue cells in the presence of cholesterol. There is no consideration of sarcoma in the case; the clinical course effectually prevents this possibility.

However, the clearcut spindle cell nature of the residual xanthoma cells is valuable in identifying this type of cell as the one predominantly concerned (mother cell) in the xanthomatous hyperplasia in our patient. It is advisable to cover this point in view of the emphasis placed at present on the reticulo-endothelial apparatus as the mother cell of the xanthoma cell. This has been particularly the case for Christian's disease, and lest the pendulum swing too far, the opportunity should be seized to maintain that this system is not the only one which is concerned in the case. Thus, for years endothelium has been considered the first type of cell liable to xanthomatous change; the spindle cell of fibrous tissue was regarded as ranking second. Even cutaneous epithelium, involuntary muscle and glia cells have been demonstrated exceptionally as participating in xanthomatous changes. One of the obstacles to the identification of the spindle cell as the type of cell undergoing xanthomatous change has been its close relation to lymphatic spaces; thus, as its nucleus rounds up while undergoing a xanthomatous

8. Virchow, R.: Xanthoma Multiplex, Virchows Arch. f. path. Anat. **52**:504, 1871.

change it becomes indistinguishable from a cell which originally may have been a plasma cell or a lymphoid cell. Occasionally, though, such a cell still maintains an elongated nucleus, and it is largely this observation which has identified the spindle cell as one of the types of cells which can act as mother cell to the xanthoma cell.

On the other hand, in the regressing xanthomatous lesions which we observed the aforementioned processes occurred in the reverse order; that is, instead of acquiring lipoid substance, the lesions were losing it. It was possible to observe more or less polygonal cells which still contained xanthomatous vacuoles and in which the nuclei were returning to an elongated form; and under these different conditions it developed that such transitional cells were not restricted to the isolated individual lesions with which we previously had to contend but were present in sizable areas. Furthermore, they adjoined narrower and broader bands of fibrosarcomatoid tissue such as has been mentioned so as to leave no doubt of the identity of the two types of cells (fig. 9). In short, the spindle cells behaved differently as the xanthomatous change regressed than as it progressed. The process took place in such a direction that, first, greater numbers of cells [9] remained enlarged simultaneously in the same retrogressive steps, and, second, the nuclei assumed their telltale form so promptly that lipoid vacuoles remained behind to identify the cells as xanthomatous.

It is also certain that xanthomas had regressed in the larynx as they had been observed clinically but were absent at necropsy. In a less conspicuous way, then, the same histologic and other processes may be assumed to have taken place, in principle, in the larynx and in the skin. The normal lymphadenoid infiltration complicated the picture at times, but nevertheless the young hyperplastic type of spindle cell remained as evidence that the same order of changes was operative in the larynx and in the skin.

Corneal lesions have also been known to regress and to recur (Pusey and Johnstone [10]).

INTERMISSIONS IN HYPERCHOLESTEREMIA

The course of the values for blood cholesterol in our patient has already been indicated in some detail; the content was first normal, then high, and finally normal again. These variations must not be regarded as errors of observation of technic; they reflect a varying cholesterol (and probably also general fatty) metabolism.

9. This afforded increased opportunity for study.

10. Pusey, W. A., and Johnstone, O. P.: A Case of Xanthoma Diabeticorum and Lipoma Multiplex and a Case of Xanthoma Approaching the Diabetic Type with Diabetes Insipidus, J. Cutan. Dis. **26**:552, 1908.

Normal prototypes of such variations are found in the hypercholesteremia of pregnancy, menstruation and the climacteric (Brown and Howard,[11] Posner [12]). In pathologic conditions they have been frequently recorded. The values for fat, in general, vary in diabetic patients under treatment. Schmidt [13] observed a drop from 706 to 162 mg. per hundred cubic centimeters in a girl with juvenile xanthomatosis. In another patient he observed values of 148, 392 and 414 mg. per hundred cubic centimeters, but he could not secure definite information as to the relation to menstruation. Incidentally, the first two of these determinations occurred only eight days apart, and they demonstrate how rapidly the change may be effected. Schmidt stated the belief:

> . . . in every xanthomatosis there was at some time a hypercholesterolemia. . . . Under certain circumstances, a renewed surge of cholesterol can take place out of its depots, whereby an increased quantum of cholesterol leads to a spilling over into those parts of the skin which are predisposed.

Our experience influenced us to agree with that belief.

In diabetic xanthoma the reflections of these variations have been expressed clinically many times by exacerbations and remissions of the lesions of the skin. In Wijnhauson's [14] case of persistent (traumatic) pancreatitis there were repeated outbreaks of xanthomatosis preceding and signaling the abdominal crisis. While there were no data as to the values for cholesterol, glycosuria accompanied the eruption.

Kirch [15] stated that certain xanthomatous tumors are not themselves responsible for the attendant hypercholesteremia, i. e., sources of cholesterol; in a case of fibrosarcoma and in two cases of lymphangioma there was not any "intermittence" in the cholesterol concentration of the blood after removal of the tumors. Ten, three and six years after removal the values were 255, 313, and 256 mg., respectively, per hundred cubic centimeters.

XANTHOMATOSIS OF MUCOUS MEMBRANES

An unexpectedly representative series of cases of lesions in the mucous membrane was uncovered in the literature. As in our case, a perianal distribution has been rather commonly noted, but it is doubtful

11. Brown, T. R., and Howard, J. T.: Xanthoma Multiplex, Internat. Clin. **4**:106, 1931.

12. Posner, O.: Symptomatic Xanthoma in Chronic Icterus, Deutsche med. Wchnschr. **35**:96, 1909.

13. Schmidt, E.: The Xanthoma Question, Arch. f. Dermat. u. Syph. **140**:408, 1922.

14. Wijnhauson, O. J.: Xanthomatosis in Recurrent Pancreatitis, Berl. klin. Wchnschr. **58**:1268, 1921.

15. Kirch, E.: Xanthomatous Tumors, Klin. Wchnschr. **3**:1425, 1924.

whether this distribution qualifies as mucosal. The laryngeal involvement, which also occurred in our patient, is naturally the most important.

Larynx and Trachea.—At least four cases besides our own have been described; several were observed at necropsy. Moxon [16] observed the yellow patches in the epiglottis and at the bifurcation of the trachea. They appeared like "white paint just under the surface." They were not confirmed microscopically, but the patient had similar patches on the capsule of the spleen and xanthomas on the hands, scrotum, back, ears, cheeks and eyes. Pavy and Fagge [17] reported having observed a patch on either side of the vocal cord. There were other lesions all along the trachea, occurring as transverse bars over the cartilaginous rings, mostly posteriorly. They extended up to the bifurcation. Xanthomatous infiltrations occurred also in the intima of the aorta, pulmonary artery and mural endocardium. There were xanthomas of the eyes, hands and abdomen. While microscopic examinations disclosed fatty changes in the skin, mucosa and tendons, such changes in the arteries were not described adequately to make it possible to distinguish between atheroma and genuine xanthoma; the gross observations were the ones of value. Pusey and Johnstone's [10] patient was studied clinically only; as in our case, the features relating to the metabolism of carbohydrates were scanty or absent, while the cutaneous lesions were of the diabetic type. The stenosis of the larynx became so great as to necessitate tracheotomy.

In Finney's [18] patient, aged 27, the symptoms resembled those in our patient in regard to the dermatologic features (involvement of the axillae and scrotum among other regions) and to the polyuria. There were many yellow patches on the pharynx. The epiglottis was scarred and deformed so that the glottis could not be seen. As viewed through the tracheotomy opening, it was yellowish, like the pharynx. A biopsy confirmed the diagnosis of xanthoma.

In Urbach's [19] patient, the larynx was yellow for another reason, i. e., hyperplasia of the elastic tissue; this is reported in full on page 804. It will be recalled that there was also hyperplasia of the elastic tissues in the retropharyngeal tendon of our patient.

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16. Moxon, W.: Simple Stricture of the Hepatic Duct, Causing Chronic Jaundice and Xanthelasma, Tr. Path. Soc. London **24**:129, 1873.

17. Fagge, C. H.: General Xanthelasma or Vitiligoidea, Tr. Path. Soc. London **24**:242, 1873.

18. (*a*) Finney, W. P.: Xanthoma Multiplex with Involvement of the Upper Part of the Respiratory Tract, Proc. Staff Meet., Mayo Clin. **6**:667 (Nov. 11) 1931. (*b*) Finney, W. P.; Montgomery, H., and New, G. B.: Two Cases of Xanthoma Multiplex Involving the Upper Respiratory Tract and Associated with Diabetes Insipidus, J. A. M. A. **99**:1071 (Sept. 24) 1932.

19. Urbach, E.: True Xanthoma or Xanthomatous Degeneration of the Skin, Klin. Wchnschr. **2**:542, 1923.

Eyes.—Beside lesions in the larynx Pusey and Johnstone's patient exhibited tumors (the largest being 1 cm. in diameter) on the conjunctiva, covering both the cornea and the sclera. They regressed and recurred from time to time. At a clinical presentation before a dermatologic society, the occurrence of "typical xanthomatous lesions in the sclera" was mentioned in reference to Schwartz and Busman's Negro patient. Legg [20] saw one such lesion in the palpebral conjunctiva.

Virchow [8] reported the presence of such lesions on the cornea and gave a detailed description of their microscopic appearance. One cornea exhibited only a diffuse patch; the other, a nodule. He cited the observations of Graefe; in two patients blindness resulted. Even at that time and to such an authority as Virchow the xanthomatous lesion was as puzzling as it is now to modern histopathologists; in places the lesion was so richly cellular as to have a "completely sarcomatous character."

Mouth.—The gums [21] are probably rather frequently involved. In Weidman and Stokes' young patient the xanthomatous infiltration occurred comparatively deeply, i. e., in the scars around the sites of extractions of teeth. Otherwise they appear to have been simply patches; such patches occurred over or above the canines and incisors in the cases of Smith [22] and Futcher [23] and on the hard and soft palate in that of Posner; [12] in the latter case the vagina and cervix were also involved. Hardaway [24] did not specify what mucosal parts—whether oral or otherwise—were involved in his case. In all these cases the cutaneous xanthomatosis was extensive, and jaundice and other evidence of grave hepatic disease were present. In general, mucosal lesions occurred mostly in the more severe xanthomatous states with visceral involvement. Futcher's patient was cured on having gallstones removed. Rosler [25] did not indicate which portion of the oral mucous membrane was affected in his patient. Pusey and Johnstone's patient also exhibited nodules in the tonsils, uvula and inside of the lips. Legg observed nodules along the margin of the tongue and as two small patches on the mucosa of the lower lip, like the patches on the skin. Crocker [26]

20. Legg, J. W.: Xanthoma Multiplex, Tr. Path. Soc. London **25**:155, 1874.

21. Weidman, F. D., and Stokes, J.: Extensive Xanthoma Tuberosum in Childhood Due to Infectious Cirrhosis of the Liver, Am. J. Dis. Child. **53**:1230 (May) 1937.

22. Smith, W. F.: Xanthoma, or Vitiligoidea, J. Cutan. Med. **3**:241, 1869.

23. Futcher, T.: Xanthelasma and Chronic Jaundice, Am. J. M. Sc. **130**:939, 1905.

24. Hardaway, W. A.: Xanthoma Multiplex of Skin Mucosae, J. Cutan. Dis. **2**:353, 1884.

25. Rosler, H.: Xanthoma Planum and Tuberosum in Chronic Icterus, with Enlargement of Spleen and Liver, Berl. klin. Wchnschr. **49**:964, 1912.

26. Crocker, H. R.: Diseases of the Skin, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1908, p. 742.

reported a yellowish white patch embedded in the tip of the tongue of a child 3 months old. Presumably it was solitary, since no information is given as to the presence of similar nodules in the skin or elsewhere.

Vagina and Cervix.—Posner [12] observed prominent plaques on the uterine cervix and maplike patches on the vaginal wall similar to those in the mouth.

Prepuce.—Hillairet [27] described a large, irregular streak on the preputial mucosa analogous to the (plane) lesion on the patient's lids.

ASSOCIATION OF CANCER AND XANTHOMATOSIS

In addition to our case we have found four instances in which a combination of cancer and xanthomatosis occurred. Petri's [28] case of xanthomatous hemangioma in the muscular wall of the ilium is remote, but deserves mention. It concerned the endothelium of varicose vessels in an involuntary muscular stroma. The condition was incidental to cancer of the gallbladder and may have represented a purely local xanthomatosis, since cholesterol is frequently deposited around hemorrhagic areas and probably near other foci of blood stasis. Determinations of the blood cholesterol were not made, but the presence of hypercholesteremia could be understood in view of the deep jaundice.

The second case, that of Weidman and Boston,[1] concerned a hypercholesteremic subject with extensive cutaneous xanthomatosis and a minute adenocarcinoma of the duodenal papilla. The blood cholesterol ranged above 1,000 mg. per hundred cubic centimeters.

A third case was mentioned by Petri; [29] in this case, however, the lipid processes concerned only the gastric carcinoma. Details will appear in a succeeding paragraph.

The fourth case is admissible provided Gaucher's disease can be regarded as xanthomatous. Pick [30] found a cancer of the hepatic duct in a subject who died of osseous Gaucher's disease. The skin was not involved.

Our case is the fifth. Of these cases, that of Weidman and Boston and ours are strongest because hypercholesteremia was associated and the xanthomatosis was unequivocal and extensive. We are not certain as to the cholesterol affinities in Pick's case; kerasin is the substance concerned in the Gaucher cell. In Petri's cases the xanthomatosis was

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27. Hillairet: Vitiligoidea, Xanthelasma, Xanthoma, Bull. Acad. de méd., Paris **7**:1166, 1878.

28. Petri, E.: Xanthomatous Tissue Changes; Haemangioma Xanthomatosum, Zentralbl. f. allg. Path. u. path. Anat. **34**:1, 1923.

29. Petri, E.: Ein Beitrag zur Kenntnis der sogenannten Schaumzelltumoren, Frankfurt. Ztschr. f. Path. **27**:507, 1922.

30. Pick, L.: The Skeletal Form of Gaucher's Disease, Veröffentl. a. d. Kriegs- u. Konstitutionspath. **4**:3, 1927.

local, and this to a certain extent weakens the significance of the association. But, in any event, the coincidence of even two instances of cancer with such rare incidents as necropsies on patients with xanthoma can scarcely be explained as an accident. We shall endeavor to indicate additional evidence in a succeeding section bearing on the rôle of cholesterol in cancer.

FATTY CHANGES OF EPITHELIUM, INCLUDING CANCER

Under this heading it is proposed to collect instances of xanthomatous changes of epithelial cells and to discuss also the simple (noncholesterol) fatty changes of epithelium so far as they pertain to the xanthomatous ones. At the outset, the capacity, pure and simple, of epithelium to exhibit fat need not be discussed; "fatty infiltration" and "fatty degeneration" call up a long list of organs and tissues which are affected by fatty changes. As to these two kinds of fatty change, however, since the xanthomatous changes commanding our interest concern not degenerate, but comparatively normal, cells, we are at once confined to "fatty infiltration" (as it parallels xanthomatous changes). In turn, we are now confined to the liver as the sole epithelial organ or tissue in the body which notably exhibits fatty infiltration. Fatty infiltration is virtually not known to have occurred in the epithelial cells of the kidney, pancreas, gastro-intestinal tract, reproductive system, thyroid gland and important glandular structures as part of a generalized disease. The epiderm and oral mucosa also belong in this list. In short, epithelium is not liable to "fatty infiltration" to the extent that cells of the connective tissue series are; incidentally, nerve and muscle cells likewise are practically immune to fatty infiltration.

In regard to xanthomatous infiltration one finds that the lines are not as strictly drawn. In cutaneous xanthomas the epiderm is commonly infiltrated by fat, and one of us has demonstrated the presence of fat in involuntary muscle, nerve trunks and glia cells (Weidman and Freeman [31]); i. e., tissues representative of all four classes of body tissue may be affected. It is true that fat may appear in the nondegenerate epiderm in diabetes mellitus, consistent with the lipemia (Weidman [32]), and we believe that an even wider distribution of "nondegenerate" fat would be detected on systematic search of other tissues of lipemic subjects, such as those with diabetes. But these conditions are at the borderline, if not within the sphere, of the lipemia-xanthoma complex. In any event, epithelium may be regarded as more liable to

31. Weidman, F. D., and Freeman, W.: Xanthoma Tuberosum, Arch. Dermat. & Syph. **9**:149 (Feb.) 1924.

32. Weidman, F. D.: Pathology of the Yellowing Dermatoses, Arch. Dermat. & Syph. **24**:954 (Dec.) 1931.

fatty changes incident to excesses of cholesterol, such as the cholesterol cramming of animals and the large white kidney in Ebstein's nephrosis, than to ordinary fatty infiltration. Indeed, in searching the literature one finds that in rare cases cholesterol infiltration may extend even to carcinomas.

CYTOLOGY OF XANTHOMATOSIS ASSOCIATED WITH CANCER AND OTHER MALIGNANT CONDITIONS

The Hypernephroma.—This probably stands as a "normal prototype" of the xanthomatous cancer. Certainly its mother cell is fundamentally cholesterophilic, and it would be surprising if the tumor were not yellow and fatty. This is, of course, conceded by all; hence it is curious that a yellow tumor involving the region of the kidney is designated as a xanthoma in the ordinary sense. Indeed, when Dietrich [33] submitted his case of "fibroxanthoma of peculiar distribution," the alternative diagnosis of hypernephroma does not appear to have been considered. Thus, he reported having found at necropsy a retroperitoneal tumor infiltrating both kidneys and also the right adrenal gland, and enclosing most massively the pancreas and the left adrenal gland. The structure of the kidney was scarcely recognizable on the right side; that organ had become fused with the adrenal gland and a general retroperitoneal mass; it was yellow-streaked. Metastases occurred to the surface of the peritoneum; and there were multiple nodules over the pericardium and the parietal and valvular endocardium, and in the papillary muscles. There was a tumor in each orbit on the optic nerve and one at the base of the brain. The cranial sinuses were more or less "completely filled with tumor masses." This was a widespread metastasis indeed; such infiltration of cardiac muscle is seldom matched except by melanotic sarcomas and hypernephromas. We believe that the foregoing description could well describe the performances of hypernephroma.

Histologically, the appearance was reported to be the same in all the regions examined. The excellent color plate of sections stained by sudan III as well as by hematoxylin and eosin leaves no doubt as to the xanthomatous nature of the tumor cells. The xanthomatous changes were so highly developed, however, that the histologic changes of hypernephroma could well have been submerged.

This tumor satisfied the requirements, morphologically, of xanthomatous change (Dietrich made detailed differential staining tests for fat and other lipoids besides making a quantitative analysis of the cholesterol in the tissues). He found 11.02 per cent of free and 16.04

33. Dietrich, A.: Ueber ein Fibroxanthosarkom mit eigenartiger Ausbreitung, Virchows Arch. f. path. Anat. **212**:119, 1913.

per cent of combined cholesterol. The lecithin content amounted to 1.8 per cent. As the cells of the adrenal glands normally elaborate cholesterol and other lipids, this case is robbed of the significance (in the way of radical alteration of fat metabolism) which attaches to other epithelial tumors, the cells of which do not ordinarily do this. We believe, though, that on the basis of the histologic illustrations there was an exaggerated production of lipids in these cells; perhaps one should go no further, however, than to think of them as superxanthomatous examples of the normal prototype of the xanthoma cell. In any event, one may regard the Grawitz tumor as the prototype of xanthocarcinoma.

At the same time, we should mention that other lipid-secreting gland, the sebaceous gland, as a structure the cancer cell of which (provided it contained cholesterol and/or other xanthomatous lipids besides neutral fat) would serve as a normal prototype of xanthocarcinoma. The (xanthoma) sense here is that of the non-neutral fat as against the preponderating normal secretion of neutral fat by this gland. This presupposes, of course, a vicarious "secretion" of cholesterol and/or other lipids which is readily understandable in such an anarchist structure as the cancer cell. Actually, Corten [34] reported such an incident. A tumor of the buttock of one year's duration was observed in a woman of 67. It was the size of the fist and easily pushed around. The regional lymph nodes were enlarged, but there was no recurrence. Not all the cancer cells were xanthomatous (undifferentiation?), but in others anisotropic droplets and other observations, together with the numerous illustrations, satisfy us that the growth was a tumor of a sebaceous gland. This is dangerous ground, in view of the original mistake of regarding xanthomas as abnormal structures of sebaceous glands; but Corten took pains to establish the fact that the tumor partook of the nature of a sebaceous gland.

Corten pointed out (the explanation holds good also for hypernephroma) that the cause of the xanthomatous change in his tumor was to be found in the cells themselves, which, as the derivatives of sebaceous gland rests, have the capacity to develop into xanthoma cells. That is, the cells of these two tumors can become xanthomatous independently of hypercholesteremia or of a surrounding local hypercholesterosis.

After these considerations, thoughts turn to other glands which normally secrete fat, such as the mammary gland and the sweat glands. We found record of but one xanthocarcinoma of these structures; that is, Corten cited briefly a metastatic mammary cancer in the adrenal

34. Corten, M. H.: Beitrag zur Histogenese des Xanthoms, Frankfurt. Ztschr. f. Path. **23**:389, 1920.

gland which became xanthic; metastases elsewhere were not xanthomatous. While it is inviting to see in this an innate property of mammary cells to continue their production of fat in the cancer, the lipoid environment (adrenal tissue) is a far weightier circumstance owing to the possible absorption of lipid. This particular cancer should be denominated a "xanthomatous cancer" rather than a fundamentally constituted "xanthocarcinoma."

Xanthocarcinoma of the Prostate.—Xanthic phases have been fully authenticated here. Schlagenhaufer [35] observed six cases; in two the regional metastases were also xanthomatous. Kinoshita's [36] report of "a number of such cases" was also convincing; his color plate shows sections stained with sudan III. Kawamura is also cited as having reported cases. The values for blood cholesterol do not appear to have been determined in these cases, but chemical analyses (Schlagenhaufer) disclosed that the fats in the tumors were not cholesterol esters.

Naturally, for cells immersed in testicular secretion a lipid content could be expected owing to the high cholesterol content of spermatozoa, but actually such a content was not demonstrated. Posser (cited by Schlagenhaufer) reported the presence of much lecithin (anisotropic material in general) in the prostatic secretion, yet such material could not be seen in normal prostatic epithelium and was present only sparingly in that of hypertrophied prostates. Therefore, the anisotropic matter must be the product of a functionally distorted cell. He emphasized that these prostatic cells were not degenerate. Even in the face of a diabetic lipemia of such grade that the blood was milky and xanthomatous deposits were widespread in the viscera, the prostate escaped in Bross' [37] case; only in certain of the glands could droplets of fat be found.

Xanthocarcinoma of the Stomach.—The stomach was the only remaining organ in which we could authenticate a true xanthocarcinoma. In Petri's [29] case the liver and glandular metastases as well as the primary lesion had a peculiar opaque, yellowish white appearance. Again, anisotropic bodies were not found in fresh material, but "granules, drops and droplets" stained alike with sudan III, chlorophyll and dimethylamido-azobenzene. It was concluded that neutral fat only was concerned in the foam cells of this tumor and that the genesis of the fat was due to a process specific for this particular type of tumor cell.

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35. Schlagenhaufer, P.: Anisotropic Substances in Prostatic Carcinoma, Verhandl. d. deutsch. path. Gesellsch. **13**:332, 1909.

36. Kinoshita, M.: Carcinoma xanthomatodes prostatae, Ztschr. f. Urol. **14**: 193, 1920.

37. Bross, K.: Generalized Xanthomatosis, Virchows Arch. f. path. Anat. **227**:145, 1920.

We appreciate that this xanthocarcinoma was not a xanthoma in the strict sense of the word, as the yellow features were not due to lipids. Instead, it represented fatty infiltration of epithelial cells, something most unusual in general pathology. However, it is included in this study as a xanthocarcinoma because it will be indexed as such in the medical literature and should be discussed in connection with our subject.

Spurious Xanthocarcinoma.—The growths catalogued by Kirch [15] as xanthocarcinomas will not stand analysis when viewed from the strict "epithelial cell" standpoint. They are spurious xanthocarcinomas. Dubs' [38] experience with uterine mucosa concerned only its stroma. Hedinger's [39] demonstration of a pathologic specimen fell far short; there was nothing to indicate that the xanthic change was in the epithelium of his "fibro-adenoma intracanaliculare lipomyxosarcomatodes xanthomatodes mammae."

Kneringer and Priesel [40] in reporting a case of "lympho-epithelioma thymi" described extensive lipoid infiltration "in many places" in their sections; it involved both the connective tissue stroma and the tumor cells. Kneringer and Priesel conducted careful differential tests for fat on the cells, and there could be no doubt about their lipid content. Values for blood cholesterol were not determined, and as the authors commented on the presence of hemorrhagic areas surrounded by cholesterol crystals, the way is clear to classify the process as local xanthoma, i. e., absorption from tissue fluids in the environment.

After that, even the epithelial moiety of the lympho-epithelioma can be questioned. Figure 3 of Kneringer and Priesel's article does not bear out the impression of epithelioma; furthermore, their notation of a "syncytium-like" arrangement of the epithelial cells is quite in harmony with the traits of the commonplace xanthoma cells of connective tissue origin. There were no metastases, and the authors themselves commented on the low grade of the malignancy, which is surprising for cancer of an internal organ. It is altogether possible that the xanthoma cells represented the endothelial moiety of an important reticulo-endothelial structure like the thymus. The absence of metastases does not bear out one view or the other with finality, as it is conceivable that xanthomatous infiltration of epithelial cells could connote impairment of their malignant propensities in the same way that infiltration of connective tissue cells is associated with impaired malignancy in xan-

38. Dubs, I.: Xanthomzellenbildung in der Uterusschleimhaut bei Fundus-Karzinom, Zentralbl. f. allg. Path. u. path. Anat. **34**:145, 1923.

39. Hedinger, E.: Fibroadenoma intracanaliculare lipomyxosarcomatodes xanthomatodes mammae, Schweiz. med. Wchnschr. **53**:828, 1923.

40. Kneringer, E., and Priesel, A.: Ein Beitrag zur Kenntnis der Thymome (Lymphoepithelioma thymi), Virchows Arch. f. path. Anat. **241**:475, 1923.

thosarcoma, although the genuinely xanthomatous cancer of the prostate can extend to regional lymph nodes. While, then, this lympho-epithelioma may still represent a genuine instance of xanthomatous change in cancer cells, there is a large element of doubt in the case.

Suzuki's [41] report of a case of "xanthoma-like tumor of the thymus gland" is not available to us for original reference.

Ganglioneuroma Xanthomatosum.—Beitzke [42] found such a tumor at necropsy in the cerebellopontile angle; it was of the size of an egg and grayish brown with yellow fleckings. The amount of cholesterol in the blood had not been determined. Painstaking histologic studies led the author to conclude that the xanthoma cells were not the result of degeneration of surrounding nerve tissue (local xanthomatosis); such degeneration did not exist. His article was not illustrated, and it is not quite clear whether the xanthomatous cells that he saw were ganglionic. The application to Beitzke's case of tumors of the acoustic nerve, which will be discussed later in this article, is clear; xanthoma cells of neurofibromatous nature could exist in Beitzke's as well as in Henschen's [43] tumor of the cerebellonpontile angle. After that, it would be a valuable histologic feat to trace transitions between such cells and ganglion cells; if the attempt is successful, it is so important that it should be recorded by illustrations.

RÔLE OF CHOLESTEROL IN THE DEVELOPMENT OF CANCER

The thought of the rôle of cholesterol in the development of cancer forces itself into consideration in view of scattered reports which collectively suggest a possible rôle of this substance in the formation of tumors. Sweet, Corson-White and Saxon [44] found that the number of "takes" in rats after experimental implantations of cancer was tremendously increased when cholesterol was distributed on the explant. Many years ago Luden [45] studied the influence of cholesterol metabolism on cancer and pointed out the necessity of taking this factor into consideration when studying cancer. In fact, it is thoroughly established by now that cholesterol promotes at least a multiplication of cells.

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41. Suzuki, J.: On One Case of Xanthoma-Like Tumor of the Thymus Gland, Tr. Jap. Path. Soc. **20**:785, 1930.

42. Beitzke, H.: Ueber ein Ganglioneuroma xanthomatosum, Beitr. z. path. Anat. u. z. allg. Path. **69**:400, 1921.

43. Henschen, F.: Zur Histologie und Pathogenese der Kleinhirnbruckenwinkeltumoren, Arch. f. Psychiat. **56**:20, 1915.

44. Sweet, J. E.; Corson-White, E. P., and Saxon, G. J.: Relation of Diets and of Castration to the Transmissible Tumors of Rats and Mice, J. Biol. Chem. **15**:181 (July) 1913.

45. Luden, G. M.: The Blood Cholesterol, Its Importance, and the Value of Its Determination in Cancer Research, Canad. M. A. J. **12**:147, 1922.

Roffo [46] added to the evidence when he reported the presence of three times as much cholesterol in tumor tissue as in the rest of the animal, and more recently Morelli and Focosi [47] again brought lipoid metabolism into the picture. The latter pointed particularly to the rôle of the lymphatic apparatus and reticulohistiocytic system, stating that their lipoids were of high significance in the formation of neoplasms. Singularly, the article immediately preceding that of Morelli and Focosi dealt with the rôle of nerve trunks (regenerating) in promoting cancer growth (Larionow and Meissel [48]); we should point out that the sciatic trunk contains medullated fibers which at once involve lipids.

Whatever the true rôle of cholesterol may be, the fact remains that the lipoid substances are in cancer seldom expressed morphologically as cytoplasmic droplets; i. e., xanthoma cells are seldom discovered within the essentially neoplastic elements of cancer.

NONDIABETIC INTOLERANCE FOR DEXTROSE

We have already indicated that diabetes was suspected at an early date in our patient on account of the erythematous character of the cutaneous xanthomas and that in the absence of glycosuria and hyperglycemia a test of dextrose tolerance was performed in order to probe further the foundation for our surmise about the diabetic factors in the case. The finding of a disturbance of dextrose tolerance—in view of our ignorance of the presence of gastric carcinoma—was interpreted as support of a diabetic (rather subdiabetic) basis for the changes.

In the new light, however, i. e., the presence of gastric cancer, we are compelled to take heed of the rôle of the cancer in accounting for the disturbed dextrose tolerance. Years ago Friedenwald and Grove [49] reported a consistent decrease in dextrose tolerance in subjects with gastric carcinoma. True, they found that a reduction also obtained in patients with cancer of other regions; however, the curve obtained for the patients with the latter type of cancers was intermediate between that for normal persons and that for patients with gastric cancer. The curve was so typical that Friedenwald and Grove invoked a decrease in dextrose tolerance as an aid in diagnosis of gastro-intestinal cancer.

46. Roffo, A. H.: Cholesterol Ratio in Tumors, Prensa méd. argent. **11**:1060, 1925; **11**:28, 1924.

47. Morelli, E., and Focosi, M.: Changes in Lipoid Metabolism Following Treatment with Cancer-Forming Substances, Ztschr. f. Krebsforsch. **34**:473 (Oct. 17) 1931.

48. Larionow, L. T., and Meissel, M. N.: Transplantation of Carcinoma (Ehrlich's Culture) into Regenerating Nerve Trunk of White Mice, Ztschr. f. Krebsforsch. **34**:429 (Oct. 17) 1931.

49. Friedenwald, J., and Grove, G. H.: Blood Sugar Tolerance Test as Aid in Diagnosis of Gastro-Intestinal Cancer, Am. J. M. Sc. **160**:313 (Sept.) 1920.

It is only fitting to record these findings in view of the gastric cancer in our case and of the fact that the decreased dextrose tolerance constituted the only evidence that could be mustered in support of a true diabetic factor. Figure 13 illustrates the situation.

It appears that in other hands the test has not been as successful as in those of Friedenwald and Grove and that it has not gained place in diagnostic medicine at large. However, whereas the results of a test of this sort may not be sufficiently pronounced in the positive direction to be of diagnostic value, they nevertheless reflected an abnormal biologic

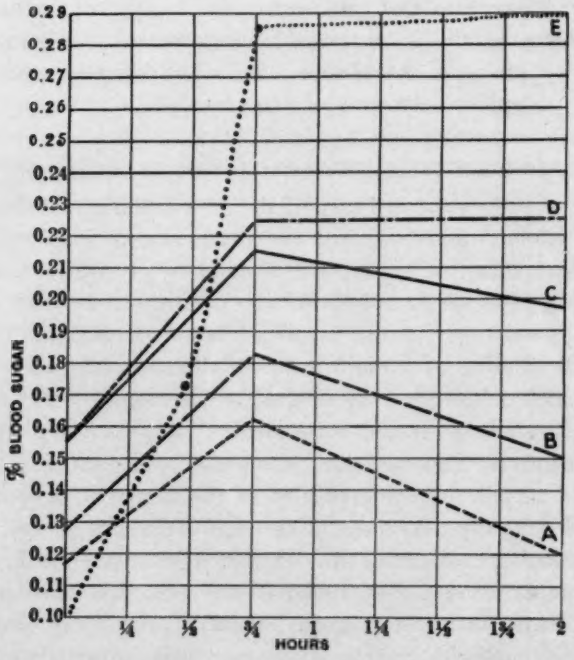

Fig. 13.—Curves showing the dextrose tolerance in various conditions. *A*, normal curve; *B*, atypical normal curve; *C*, intermediate curve; *D*, curve for cancer; *E*, curve for xanthoma.

state that was genuine and that was sufficient to confuse us for a long time. Our experience may stand in good stead for others who may become similarly puzzled, and it may turn their attention toward the seeking of a definite explanation.

PSEUDODIABETIC XANTHOMA

This term is proposed for the xanthomatous symptom complexes which, as in our patient, include cutaneous xanthoma diabeticorum but lack the essential disturbances of carbohydrate metabolism signified by

glycosuria and hyperglycemia. As to true diabetic xanthoma, a fairly complete knowledge of its cutaneous expression prevails. This is due to a notable series of reports of cases, in spite of the fact that even those in charge of large clinics for diabetic patients agree that xanthomatous lesions appear comparatively rarely even in such a large experience. Details of the dermatologic features may be found in Mook and Weiss'[50] comparatively recent article. For our purposes, i. e., for comparison with the conditions hereafter discussed, it suffices to recite simply the features which are pertinent to our case: There is no consistency as to the distribution; whereas lesions tend to appear on the elbows, knees and buttocks, as in nondiabetic xanthoma, there are frequent exceptions. The eyelids are commonly not affected, yet Pusey and Johnstone reported an exception. Furthermore, they emphasized that Pollitzer, Darier and Crocker had separately reported cases of a condition intermediate between xanthoma tuberosum and xanthoma diabeticorum. Occasionally lesions in the axillae and around the anus are encountered, something that is unknown, or at least rare, in ordinary xanthoma tuberosum.

The outstanding differential diagnostic feature of diabetic xanthoma, and one that is present in pseudodiabetes, however, is the essentially inflammatory nature of the papules; they invariably begin as red, inflammatory lesions; the yellow xanthomatous features are superimposed secondarily and appear as a cap at the summit of the papule. This frequently leads to the mimicry of pustules. Stated in another way, the presence of inflammatory areolae around the xanthoma lesions is practically diagnostic of diabetic xanthoma. These areolae have a further peculiarity in the rapidity with which they appear: They are multiple and are at first comparatively uniform in size and small; as the glycosuria improves under treatment, they regress. Larger lesions, i. e., those containing greater masses of cholesterol, regress more slowly or may even remain permanently.

The internal changes accompanying diabetes need not be repeated here; of course, hypercholesteremia may be detected, and several instances of associated tuberculosis have been reported (Bross[37]). Kirch has indicated how the amount of cholesterol in the blood can vary in patients with xanthoma in general, and similar variations may occur in the diabetic form (see succeeding paragraph in this article).

Our own patient's condition compares rather poorly with this description, particularly in the essentially diabetic aspects. It is true that the cutaneous lesions were definitely inflammatory; the condition was originally diagnosed as erythema telangiectodes and parapsoriasis.

50. Mook, W. H., and Weiss, R. S.: Xanthoma and Hypercholesterinemia, Arch. Dermat. & Syph. **8**:19 (July) 1923.

Furthermore, the lesions regressed. Again, the perianal and axillary regions were involved. On the other hand, discrepancies from the internal medical point of view were met in the inconstancy of hypercholesteremia, the questionable presence of glycosuria (only on one occasion) and the absence of hyperglycemia, all of which are weighty objections. The polyuria and polydipsia, on the other hand, and the very definite dextrose intolerance (see succeeding paragraph) at once added items to the diabetes complex. In view of this dilemma it is regrettable that a section of the pancreas was not secured at necropsy, but this was not performed under our immediate control.

We are thus motivated to regard our patient as presenting diabetes, but without clearcut evidence of disturbed carbohydrate metabolism. It is emphasized that tests were made at intervals over a period of years and that ordinary abnormalities of dextrose metabolism must be excluded from the disease complex in our patient. We cannot make an outright diagnosis of diabetes mellitus. Diabetes insipidus certainly was present. We are prompted to wonder whether the condition was not indeed a disturbance of carbohydrate metabolism but one not concerning dextrose in particular; the inadequacy of methods of chemical analysis prevented us from inquiring into other phases of an upset in carbohydrate metabolism which might reveal the presence of an abnormality of dextrose metabolism. We therefore temporarily designate the condition as pseudodiabetes, although perhaps paradiabetes would be more appropriate.

Other instances of erythematous xanthoma in which defects of dextrose metabolism could not be established satisfactorily are known. Lebedew's [51] case has been cited in full in another article (Weidman [52]); in this case, again, the xanthomas were preeminently inflammatory and neither dextrose nor pentose could be demonstrated in the urine; there were polyuria and polydipsia. Interestingly, this patient had lesions on mucous membranes (namely, on the hard palate with the uvula displaced by a mass) as did our patient. By no means could a confirmation of the diabetic state be secured by examination of the blood or by other laboratory procedures. There was a general adenopathy, and histologically the xanthomatous masses of the face were regarded by Lebedew as essentially granulomatous but not gummatous or tuberculous. It is altogether possible that similar lesions were present in the pituitary region and that the condition was an example of so-called pituitary diabetes. Lebedew's patient, like ours, was emaciated—poverty

51. Lebedew, A. J.: Xanthoma Multiplex Pseudodiabeticorum with Xanthomatous Lymphadenitis, Dermat. Wchnschr. **59**:1343, 1914.

52. Weidman, F. D.: Xanthosarcoma of the Cheek Succeeding Xanthosarcoma of the Forearm: Multiple Tumors Versus Metastasis, Arch. Surg. **34**:792 (May) 1937.

stricken, as he put it—and the reflexes were exaggerated as in our patient. The distribution of the lesions was not that usually observed in diabetes, as in our patient. The cutaneous lesions cleared up after thirty-five injections of sodium arsenite (natrium arsenici). There is no statement as to a determination of blood cholesterol.

In Pusey and Johnstone's case the condition was simply labeled as diabetes insipidus; the cutaneous lesions were extensive, were of diabetic type (violaceous areolae) and exhibited regressions from time to time, as in our case. Singularly, the trachea was involved in their case as in ours.

The symptoms in Finney's [18] case paralleled those in ours in numerous respects. In a man with lesions of the axillae and scrotum, among other sites, there developed polydipsia and polyuria but without disturbances of cholesterol, dextrose or other blood components tested for. There were numerous xanthomas on the walls of the pharynx and hypopharynx. The epiglottis was scarred and deformed to the extent that the glottis could not be seen. Tracheotomy became necessary. The cutaneous lesions were not diabetic in type, and it appears that hepatic disease could be excluded. There appears to be sufficient evidence to show that fundamentally the condition in Finney's case was closely related to that in ours, if not identical with it. A second patient with a similar condition has subsequently come under Finney's [18b] care.

Stryker's [53] patient showed a normal value for blood sugar (105 mg. per hundred cubic centimeters), but there was a low dextrose tolerance, glycosuria being noted at each test in addition to the hyperglycemia. Whether primary hepatic disease was certainly present or not, gallstones were identified roentgenologically; jaundice and colicky pains were present in the upper right abdominal quadrant.

We thus have a number of instances of xanthoma in which the cutaneous manifestations suggest xanthoma diabeticorum, but in which the internal medical phases of diabetes mellitus are not completely or satisfactorily rounded out symptomatically. Hence we believe that, at least tentatively, a taxonomic separation is justified. In cases in which there is an associated hypertrophic cirrhosis of the liver, as in Weidman and Freeman's case of Christian's disease, and in cases in which such a condition was not excluded clinically, as in the cases of Lebedew, Finney, Pusey and Johnstone, and Stryker, there is not so much occasion for puzzlement because disease of the liver has long been established as the important cause of xanthoma. In our case, however, the liver was anything but cirrhotic; the disease may represent a unique form among the pseudodiabetic xanthomas as we have defined them.

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53. Stryker, J. V.: Xanthoma Diabeticorum, Arch. Dermat. & Syph. **22**:913 (Nov.) 1930.

After these considerations the relation of other instances of fatty disease to the malady of our patient is not as close. The case presentd by Tulipan [54] becomes more or less pertinent. The cutaneous lesions were described merely as pinkish yellow; however, a previous outbreak had disappeared on dietary treatment. As the patient had marked acromegaly, it was doubtful that this was a case of true diabetes; it was mentioned that in disease of the pituitary gland hyperglycemia and glycosuria such as this patient exhibited could occur. If one adds the numerous instances of Christian's disease (preeminently cerebral), in which polyuria and polydipsia have consistently been present, to the cases of pseudodiabetes which we have already mentioned, there results a considerable accumulation of evidence which, if not pointing exactly to the pituitary gland, at least congregates around the base of the brain. Perhaps it is going too far to invoke as evidence the tumors of the acoustic nerve or the pontile lesions of our patient, but even without these a sufficient sum of evidence remains to direct attention to the base of the brain in cases of such atypical manifestations.

Urbach's [19] experience interdigitates with our case because there were lesions located on the wall of the larynx and because the two patients were either diabetic or subdiabetic. Thus in the cases reported by Urbach one of the sisters (an offspring of consanguineous parents) showed dextrose in the urine, whereas it was necessary to perform dextrose tolerance tests to reveal the latent diabetes in the other. The blood cholesterol in one of these patients was 240 mg. per hundred cubic centimeters.

In these two patients the cutaneous lesions on the face were those not of xanthoma but of another fatty dyscrasia, i. e., a degeneration of fibrous tissue whereby it became hyaloid and at the same time gave quasifatty reactions with sudan III. Thus, Urbach concluded that there was a combination of fat and protein (the lesions were yellow, clinically); this assumption was necessary to account both for the fibrous qualities exhibited morphologically and for the obvious fatty ones which were indicated both grossly and by special staining for fat. Perhaps Urbach's experience broadened our ideas as to the capacities of the fatty changes possible in diabetes. Whereas in some cases gross quantities of fat are deposited, leading to the production of xanthoma, in others the process may not have advanced that far but fat may be present only in combination with protein (analogy with the large yellow kidney). Incidentally, the cutaneous lesions presented by Urbach's patient had the distribution of the dermatosis well known to derma-

54. Tulipan, L.: Xanthoma Tuberosum Multiplex and Acromegaly, Arch. Dermat. & Syph. **22**:724 (Oct.) 1930.

tologists as adenoma sebaceum, a congenital anomaly and one which heretofore has not been referred to as a general systemic fatty process.

In the light of these observations it is incumbent on the dermatologist to inquire deeply into all sorts of yellowing or fatty changes in the skin, whether they are referable to hyperplasia of elastic tissue or of other (xanthomatous) nature. He should determine the status of the blood lipids or, even further, settle the possibility of an underlying diabetic or subdiabetic state. A diabetic state is not invariably or even commonly present, but it is one of a few conditions that are possible, and one should determine the extent to which it obtains and after that decide whether a dermatosis which bears on internal states can be catalogued again and again.

RÔLE OF NERVE TISSUE (NEURILEMMA, ENDONEURIUM) IN XANTHOMATOSIS

The Tumor of the Acoustic Nerve.—It is advisable to dwell sufficiently on this type of tumor because it may have a bearing on cutaneous xanthomas just as it has been found associated with xanthomatous neurofibromas of other organs. Thoughts in this direction were prompted by the finding in our patient of the lesion in the pons, concerning which there was for a considerable time much uncertainty as to the diagnosis, both grossly and microscopically. Thus, in the absence of the yellow pigmentation it could not be referred at once to xanthoma, and obviously it was not a metastasis from the gastric cancer, as demonstrated by histologic sections. The report of a xanthomatous ganglioneuroma (Beitzke [see p. 798]) focused attention to tumors in the cerebellopontile angle; the work of Henschen [43] was responsible for the succeeding thoughts as to the possibility of a fibroneuromatous basis for some of the lesions of cutaneous xanthomatosis. We should emphasize at once that such a widespread biologic vagary as intracellular lipoidosis can scarcely be confined to a single class of cell such as the nerve cell and that, whatever may be the outcome of the present discussion, a nerve tissue basis could obtain only in a fraction of cases of cutaneous xanthoma.

To begin with the auditory nerve, it is conceded that this particular cranial trunk exercises pathologic vagaries, which in the final analysis are referable to its peculiar embryologic development. Thus, the peripheral, intratemporal parts develop from surface ectoderm and progress centrally toward the brain stem, while its mesial, preeminently intracranial portion proceeds peripherally from the brain stem. The two portions merge near the porus acusticus; at the junction there is usually a rather sharp boundary zone, on one side of which the essentially

glial structure of the brain stem is exhibited (even in adult life), whereas the more peripheral portion exhibits the structure of a medullated (fatty sheath) nerve. This region of fusion is thought to be the seat of the tumor for which the acoustic nerve is notorious. It is consistently observed, almost axiomatic in medicine, that junction planes of embryologic folds and fissures are subject to pathologic changes.

As to the tumor which develops in this region, its composition seems to have been settled by Henschen, who referred it unequivocally to the distal portion of the acoustic nerve and finally came to the conclusion that its structure is that of a neurofibroma analogous to the tumors in Recklinghausen's disease. It must be noted at the same time, however, that there is a second theory, namely that of Aoyagi and Kyuno.[55] These workers believed that the tumor of the acoustic nerve develops from certain nests of endothelioid cells which normally occur around the acoustic nerve, i. e., in the connective tissue. Henschen, on the other hand, assigned the origin of the tumor to the neurilemma or endoneurium. It is disappointing that he rather neglected the significance of these endothelioid cell nests in an otherwise monographic survey of cerebellopontile tumors. He concluded that the resultant tumor is a neurofibroma.

The importance of these different points of view in relation to the skin becomes clear from a study of figure 18 of Henschen's article, in which one of the tumors is seen to consist in great part of large, clear cells which may well be xanthoma cells; furthermore, although Henschen refrained from making the slightest hint in that direction, the cells may be modifications of the endothelial cell nests of Aoyagi and Kyuno. If to this observation one adds the fact that in no less than seven cases neurofibromatosis of the skin has been found associated with tumor of the acoustic nerve, to say nothing of more or less solitary tumors of the stomach, intestines, bronchi, etc., one is in a position to envisage a state not of local but of generalized "neoplastic" instability of peripheral nerves. Indeed, one case (Delore[56]) of associated xanthoma was cited by Henschen.

After this, the significance and application of the tumor of the acoustic nerve to the cutaneous xanthoma can be considered. Both tumors are grayish yellow or yellow. Both tumors contain, or can contain, xanthoma cells; both are preeminently benign; both may begin in early life (in one of Henschen's patients the symptoms, difficulty of

55. Aoyagi, T., and Kyuno, A.: Endothelial Cell Nests in the Dura, Neurologia, 1912, vol. 2; cited by Henschen (the original article is not available to us in the literature).

56. Henschen does not state the reference.

hearing, began in childhood); both, when not xanthomatous, may exhibit the structure of fibroma or neurofibroma. There are possibilities of regression; there is certain evidence of this in the case of lesions of the skin, but we can only speculate as to whether the pontile tumor in our patient was xanthomatous at one time.

Features which are unsettled as regarding a differentiation between cutaneous xanthoma and tumor of the acoustic nerve are as follows: There is no evidence that nerves proceed centrally from the cutaneous ectoderm and effect a connection with elements or derivatives of the central nervous system. The recent work, however, of Masson,[57] who pronounced in favor of a nervous origin of many cutaneous nevi the cells of which approach the epiderm most closely (debated nature of Langerhans' cells) should at least be noted. Furthermore, it must be recalled that cutaneous xanthomas, being localized developments, do not necessarily presuppose a widespread, consistent junction of such epidermal and central nervous components; they need be but local, comparatively anomalous and sparingly developed affairs. Perhaps phylogeny would assist in supporting this concept; the study of the embryologic development of special sense organs in lower animal forms might shed light on this question. In the light of the information which now prevails as to the tumor of the acoustic nerve, this theory of "dual origin," if proved for the skin (which also contains both ectodermal and mesodermal derivatives), would be welcome in explaining why, in certain patients, xanthomas are more common in, or are even confined to, the skin.

As a matter of fact, though, it is not necessary to insist on the hypothesis of a "dual origin" in order to avail ourselves of neurofibromatous cells in explaining the histogenesis of xanthoma. It should be remembereed that xanthoma cells are, at least in part, connective tissue cells which were destined to cover nerve fibers. Indeed, whether derived from surface or from central nervous elements, such cells by virtue of their companionship with nerve tissue at once become influenced by metabolic factors that concern lipid. The medullated nerves are coated with lipid, whether it is neurilemma or endoneurium that plays a part in its production. The suspicion is at once aroused that the nerve cells just mentioned have some sort of connection with lipid; they are at least in propinquity to it, if not actually genetically and fundamentally metabolically altered by changes in lipid metabolism. This is precisely the additional factor for which pathologists have been searching to join with hypercholesteremia in order to explain the process underlying the complete development of the xanthoma cell; it is a state

57. Masson, P.: Les naevi pigmentaires, tumeurs nerveuses, Ann. d'anat. path. 3:417, 1926.

that borders on the cholesterophilia of Siemens.[58] It is intriguing, too, that the caution with which general pathologists approach the diagnosis of neurofibroma (as it occurs apart from obvious nerve structures) is paralleled by the uncertain identity of many xanthoma cells in the skin and by the long debate as to the cytologic origin of tumors of the acoustic nerve. All these experiences with such cells, even though they occur in the tissues of adults, harmonize with the unestablished embryologic origin of neurilemma as accepted today. In the realm of neurilemma and endoneurium one is exploring a field which, embryologically and lipoidally, is still uncertainly charted, and while final conclusions must be withheld, it is still proper to practice trial and error, both speculatively and concretely.

The missing link in the chain of parallels listed for cutaneous xanthoma and tumors of the acoustic nerve consists in the absence of information as to hypercholesteremia in cases of tumor of the acoustic nerve; this phase is worthy of fuller inquiry by neurologists. It is reasonable to suppose that the occasion for at least a portion of tumors of this nerve is the infiltration of their cells by lipoid substance and that, in turn, this infiltration is finally referable in some cases to hypercholesteremia. Attention to the diet and to cognate factors may open the way to a nonsurgical ally in the treatment of some tumors of the acoustic nerve. Conceivably the endothelioid cells mentioned by Aoyagi and Kyuno (one should still regard them as possible mother cells of tumors of the acoustic nerve) can assume the characteristics of xanthoma in the absence of hypercholesteremia, just as cutaneous xanthomas occasionally occur without hypercholesteremia; however, it remains true that in the event of development of hypercholesteremia, cells potentially xanthomatous are likely finally to acquire these properties or to develop even greater expressions than previously. All of this would be momentous to the patient in the case of a tumor occupying the strategic location held by a tumor of the acoustic nerve.

Rapport Between Tumor of the Acoustic Nerve and That of the Pons.—Concerning the tumor of the pons in our patient, (1) its location and (2) its physical properties need to be examined in this new light.

1. There is theoretically a passing chance that this tumor was in principle related to the auditory nerve, as its initial fibers traversed the pons on the way from its nuclei to its peripheral distribution. This speculation, however, would be unwarranted unless it could be demonstrated that the intracranial portion of the nerve was also abnormal, particularly in the direction of xanthomatosis. But at that, it is diffi-

58. Siemens, W. H.: Ueber ungewöhnlich ausgebreitete Xanthomatose ohne Hypercholesterinämie, Arch. f. Dermat. u. Syph. **138**:431, 1922.

cult to conceive how the peripheral anlage of the acoustic nerve could send its extensions centrally to the extent that they would penetrate the substance of the brain stem.

2. The physical properties of the typical tumor of the acoustic nerve and those of the tumor in the pons must be compared. In these points we find closer agreement. Both are soft and elastic and have a moist, edematous cut surface. Henschen's description (case 37) of a tumor of the acoustic nerve, "soft elastic, . . . surface gray-red yellowish; . . . cut surface moist and sprinkled with irregular hyaline gray-white streaks, which mark off reddish-yellow, now opaque, now edematous or hemorrhagic, often cystlike regions," and "the large, opaque, yellow parts give an almost hypernephromatous appearance to the tumor," combines the description of the pontile tumor as we saw it and of one in which xanthomatous features had occurred in the past.

It is thus not a far step, but one based on sound biologic principles, to view the entire pontile-cutaneous syndrome in our patient under a common heading, i. e., as a congenital maldevelopment of neurofibromatous tissue, some foci occurring in the skin and some in the pons (corresponding to the presence in other patients of lesions of the auditory nerve), by virtue of which such cells, being cholesterophilic, under appropriate conditions became overloaded with cholesterol and constituted tumors. After that, with the resorption of the fat, the pontile tumor took on the moister, more edematous, nonpigmented qualities typical of tumors of the acoustic nerve. Such a hypothesis supplies the cholesterophilic phase which is almost a sine qua non for the development of xanthomas.

Cholesteatoma.—The lesions included under this caption have no consistent bearing on the etiology of xanthoma. The term "cholesteatoma" connotes little more than a physical state, i. e., a high content of cholesterol. Many of these "tumors" are probably merely accumulations of the same order as dermoids and residual abscesses. Even in the case of others, in which it may be suspected that epithelial cells enter into the composition, there is little likelihood that such cells become xanthomatous. There is, however, a xanthomatous element in cholesteatomas which occurs in the choroid plexus (source in endothelium?) and in those in the cerebellopontile angle. The latter, as they occur in connection with the eighth nerve, at once introduce the subject of tumors of that nerve and illustrate the extreme degree which the massive accumulations of cholesterol may reach. (This is shown in the illustration in Reimann's [58] article.) The scope of the term "cho-

58. Reimann, S.: Cavernous Hemangiomas, in Kaufmann, Edward: Lehrbuch der pathologischen Anatomie, translated by Stanley P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, p. 1840.

lesteatoma" is thus broad enough to include cutaneous xanthoma as cholesteatoma, particularly if the aforementioned "dual theory" is valid.

RELATIONSHIP BETWEEN THE GENERAL PATHOLOGIC PROCESS AND THE ORIGINAL DERMATOSIS

Under this heading we shall disregard the terminal, xanthomatous dermatosis and confine ourselves to the one which appeared earlier in the disease and was designated as parapsoriasis and erythema telangiectodes by Greenbaum. Only his painstaking description of the cutaneous changes at that time makes the present discussion possible. With this asset it is inviting to attempt to reconcile the original cutaneous symptoms and the ones subsequently added in such abundance, particularly at necropsy.

In doing this, we must, of course, confine ourselves to the pathologic processes which obtained in the earliest stages of the disease, since the cutaneous lesions referred to occurred only at that time. We cannot claim much success in formulating relationships at that time, but since xanthamotous lesions became promptly associated, a high content of cholesterol in the blood, or at least a fatty dyscrasia, should certainly be one of the conditions to be inquired into in future cases of parapsoriasis and erythema telangiectodes. After that there do not appear to be any logical leads. However, in the light of the tumors of the acoustic nerve already discussed, inquiries into nervous reflexes or other neurologic signs of vasomotor disturbance are in order; tumors of the acoustic nerve observed at necropsy have been suspected (on the basis of deafness) as early as in childhood (Henschen).

SUMMARY AND CONCLUSIONS

A highly complicated case of cutaneous xanthoma is reported. Whereas the dermatologic changes observed clinically were compatible with diabetic xanthoma, the complete formula for the diabetes mellitus complex could not be worked out. A large adenocarcinoma of the stomach and a sizable tumor (regressive xanthoma) in the pons complicated the situation. Rare observations on the larynx were recorded: it was found to be xanthomatous clinically; at necropsy it was fibrous and distorted.

Neither the gastric cancer nor the tumor in the pons was xanthomatous. Instances of xanthomatous carcinomas, valid and otherwise, are compiled from the literature and analyzed.

Involvement of the mucous membrane in cutaneous xanthomatosis (gums, larynx, hard palate, trachea, conjunctiva, vagina and cervix) occurs fairly frequently; usually it is present in the graver constitu-

tional forms with severe visceral involvement. Therefore, such an involvement carries a graver prognosis.

Hypercholesteremia was inconstant in our patient. The value for the cholesterol in the blood is modified by menstruation, pregnancy, the climacteric and antidiabetic therapy in addition to certain well known essential pathologic states.

The association of cancer and lipoidosis in our patient, as well as in three others, revives attention to the rôle played by cholesterol in some cases of cancer.

Intolerance for dextrose can occur independently of diabetes mellitus; in our patient it may have been referable to the gastric cancer.

Regressive xanthomatous lesions exhibited spindle cells in such profusion as to approach, in places, the morphologic appearance of fibrosarcoma; this stage of xanthoma pointed to fibrous tissue cells as the mother cells of the xanthoma cells in our case.

Attention is directed to the sheaths of cutaneous nerves as a possible source of cutaneous xanthoma cells and the possibility is suggested that the process is analogous to the histogenesis of the notorious neurofibroma of the auditory nerve. Such a theory would reconcile xanthomas of the acoustic nerve with those of the skin; an association of the two types of tumors has already been reported in the literature. Further information as to the association of hypercholesteremia and tumors of the acoustic nerve is needed.

The term "pseudodiabetic xanthoma" is proposed as a new name for conditions like that in our case in which the symptom complex of xanthoma diabeticorum is not completely rounded out.

In a number of cases of xanthoma, there appears to have been disease not alone in the pituitary region but independently of it in other parts of the base of the brain.

Histologic sections have been filed in the Central Bureau for Preservation of Results of Medical Research, Army Medical Museum, Washington, D. C., Accession no. 52842, and in the Laboratory of Dermatological Research, University of Pennsylvania, Accession no. 2100.

ABSTRACT OF DISCUSSION

Dr. Udo J. Wile, Ann Arbor, Mich.: The case reported by Dr. Weidman should add evidence in support of the fact which has been brought out before that in xanthomatosis one is dealing essentially not with a perversion of the cholesterol metabolism but with a disturbance of the entire lipid metabolism. The most striking thing in the case reported is the location of the tumor in the region of the pons. It may be recalled that in a communication that I made before this association some years ago it was suggested that the entire distribution of fat seems to have a central control, and from some work that has been done in California it appears that this center is located somewhere near the pons in the area of the

tuber cinereum. The stimulation of this area in rats led to an extraordinary degree of change in the development of fat. The rats showed enormous deposits of fat in various parts of the body as well as diabetes insipidus. It occurs to me that in this case the tumor in the pons, which was not carcinomatous but more or less fibrous, may have been the starting point of the irritation which led to the deposition of the xanthomatous tumors in various parts of the body. This tends to verify the fact that the control of lipid metabolism is central and located somewhere in the tuber cinereum.

My own work and that done in Dr. Bloch's clinic show that xanthomatous tumors are not necessarily cholesterol tumors and that they are not necessarily connected with a high content of cholesterol in the blood although this may at times occur; when it does occur it is associated with a profound disturbance of the entire lipid metabolism.

Dr. Paul A. O'Leary, Rochester, Minn.: I have had the opportunity to study two cases similar to the one reported by Dr. Weidman, which were reported by Dr. Montgomery, Dr. Finney and Dr. New. One of the patients died recently in Chicago, and I was informed that there was a tumor in the pons. The other patient is steadily failing; at present his incapacity is due to cardiac involvement. The only evidence of involvement of the nervous system is shown by the presence of diabetes insipidus. The roentgenographic examination showed the cardiac enlargement to be of such a type as to suggest the possibility of xanthomatous involvement of the cardiac muscle.

In the case of ganglioneuroma which Dr. Montgomery and I reported yesterday the clinical appearance of multiple xanthoma, especially in the early lesions, was seen. In a study of the section opinions differed as to whether the tumor was composed primarily of reticulo-endothelial cells (reticulo-endotheliosis or ganglion cells), and because of the many transitional types of cells noted, particularly in the involuting lesions, the significance of the reticulo-endothelial cells could not be ignored. Dr. Weidman's case indicates a relationship between the reticulo-endothelial system and xanthoma cells, while in our case the vacuolated ganglion cells in the involuting lesions could be mistaken for xanthoma cells if the Nissl granules and dendritic processes were not recognized. A search for ganglion cells should be made in tumors suspected of being xanthomatous.

Dr. William Allen Pusey, Chicago: Dr. Weidman referred to a case reported by Dr. Johnstone and me about thirty years ago and asked me to say a few words. I have not reviewed the case recently, but I remember the salient facts clearly.

The patient, a boy, came under my observation when he was about 14 years old; he continued under observation until he was 21 or 22. He did not have the emaciated type of diabetes insipidus but was rather well built and well nourished, with a juvenile, extremely pale skin. He had failed to develop sexually, but otherwise the development was normal. He had many xanthomatous lesions, some in peculiar locations. There was one in the cornea, and others were present in the larynx. An extraordinary lesion half the size of a small finger-nail, disk-shaped, occupied apparently one third of the cornea. The lesions that gave him trouble were in the larynx. The boy's physical condition became serious and the disturbance proved to be due to air hunger. A tracheotomy and the constant use of the tracheal tube brought about an improvement. As I remember, there was no appreciable or important variation either in the diabetes insipidus or in the appearance of the lesions. They remained unchanged throughout the entire period of observation. When I last heard about this patient his condition was again bad.

Dr. Johnstone and I studied at the same time a case of true diabetic xanthoma in a very obese man, who showed an enormous number of subcutaneous lipomas. The tumors disappeared completely with improvement in the sugar content of the blood; I saw the patient fifteen or twenty years later, and there had been no recurrence of the xanthomatous tumors.

Dr. Sigmund Pollitzer, New York: The case presented by Dr. Weidman is remarkable in many respects. In the first place, it is unusual to be able to follow a case through so many years, the patient having been presented by Dr. Schamberg in 1922, then thoroughly studied and made the subject of a report by Dr. Greenbaum in 1926 and then followed to necropsy by Dr. Weidman, who has given a complete analysis of the case.

I have been interested in xanthoma practically all my life. Dr. George Henry Fox may recall that at the first meeting after my election as a member of this organization in 1897, I presented a paper on xanthoma and brought out then a number of new points. Regarding the relation of xanthoma and fibrosis, the early literature is full of delusions about tumors in which fibrosis plays a rôle. Fibromatous development is the rule in xanthoma. I believe that every deposit of xanthomatous material in the skin results in time in hyperplasia of the connective tissue and that finally the growth of the connective tissue overwhelms the xanthomatous material, leaving a fibroma. In very old xanthomas the growth is hard, and microscopically it shows the structure of a fibroma, with remains here and there of a characteristic cell which takes the stains for fat that demonstrate xanthoma cells. The fact that fibrous tumors develop as a result of deposits of cholesterol not only in the skin but in many regions is well brought out in Dr. Weidman's paper. The tumor in the pons was a peculiar feature. Little is known of the metabolism which results in excessive cholesterol, but recent work seems to point to a central control of fat metabolism, and one can dimly see the relationship of a tumor of the pons to this generalized disease. Of course, tumors of the pons are not extremely rare, but only in a few cases have they been accompanied by lesions of xanthoma. I believe that this observation tends to throw a little light on the knowledge of the pathogenesis of the peculiar disease under consideration.

Dr. Jeffrey C. Michael, Houston, Texas: The formation of xanthomas interests me just now because I have been investigating the subject with Dr. Nicholas, a biochemist, at the Rice Institute. Since Dr. Wile and his collaborators reopened the question some illuminating work has been done by Dr. Schaaf and Dr. Werner of Dr. Bloch's clinic.

It is now indicated that in xanthomatosis there is a disturbance in the fat metabolism as a consequence of disease of the liver or of the central nervous system. The disturbed metabolism produces an alteration in the normal ratio of the lipid components of the blood. This results in an unstable emulsion of the blood. Such an unstable emulsion is more easily deemulsified in the tissues than normal blood. The deemulsification leads to the deposition of lipids in tissues which are altered as the result of trauma, inflammation, etc., with the production of xanthomas.

Dr. Fred D. Weidman, Philadelphia: There is only one point on which I wish to dwell further, namely, the anatomic seat of the disturbance in the patient under consideration. In xanthoma one often finds enlargements of the liver; sometimes the adrenal glands are hypertrophic, and in addition the kidneys may be large, white and overloaded with xanthomatous substance. A disturbance of the

reticulo-endothelial system was suspected, but we could not find that the endothelium at large was overloaded with lipoids. Similarly, the liver, adrenal glands and kidneys could be excluded. The remaining possibility is a new theory, namely, an involvement of the external cells of nerve sheaths as exemplified in the auditory nerve. The mere fact that the major tumor occurred in the pons does not imply that it was not still a tumor of the acoustic nerve. Neurologists have established the fact that there is a peculiar (embryologic?) instability of the cells forming the sheath of the anlage of the auditory nerve; hence this type of cell may have to be taken into consideration in studies of the derivation of xanthomatous tumors.

POSITION OF "PSEUDODIABETIC XANTHOMA" AMONG THE LIPOID DISTURBANCES OF THE SKIN (URBACH)

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When the foregoing communication by Schaffer and me [1] was submitted for publication in 1933, Urbach's publications of 1932 and 1933 had not come to our attention. Since these publications are destined to play a large part in future considerations of the cutaneous lipoidoses, it is desirable to indicate what position the condition which we described as pseudodiabetic xanthoma occupies in relation to his classification.

It should be emphasized at the outset that the term pseudodiabetic xanthoma was submitted by us as an essentially clinical designation. Urbach's nomenclature, while based partly on the clinical features, stressed the pathologic changes (extracellular cholesterosis and lipoid proteinosis).[2] Nevertheless, our case can still be fitted into Urbach's system, although our report admittedly had shortcomings in respect to some of the chemical determinations of the various lipoids concerned. On the basis of his classification, a special niche will have to be made, I feel, to accommodate the case here concerned.

Urbach [3] listed nine clinical types of cutaneous lipoidosis as follows:

General: Xanthelasmatosis
Extracellular cholesterosis
Niemann-Pick's disease

From the Laboratory of Dermatological Research, University of Pennsylvania.

1. Weidman, F. D., and Schaffer, H. W.: Xanthoma of the Skin and Larynx, Associated with Carcinoma of the Stomach and a Regressive Xanthoma of the Pons, Arch. Dermat. & Syph., this issue, p. 767.

2. It is questionable whether the policy adopted by Urbach is well advised at a time when the number of cases comprising a group is still meager, as in the case of lipoid proteinosis and extracellular cholesterosis—at least for purposes of clinical classification. It is conceivable that these forms of change in the tissues may be met later under quite different clinical circumstances. In the case of the xanthelasmas and resorption xanthelasmas, for which great numbers of case reports act as guides, it is different. It appears to us that Urbach's classification, which is extremely valuable now, is more or less temporary and will be readjusted as the changes of the various lipoid disturbances are rung on patients with this or that systemic peculiarity (constitution, allergy or complicating metabolic fault).

3. Urbach, E.: Lipoid Metabolic Diseases of the Skin, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 2, p. 238. A valuable abstract appears in Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1934.

Hepatosplenomegalic skin and mucous membrane lipoidosis
Lipoid proteinosis
Gaucher's disease

Local: Resorption xanthelasmas
Necrobiosis lipoidica diabeticorum
Imbibitio lipoidica telae elasticae degeneratae

At once two fields of inquiry for determining the fundamental nature of the pathologic processes in our case as compared with Urbach's system appear: (1) such gross features as clinical course, symptoms and anatomic distribution (and type) of the lesions; (2) histologic and chemical features, especially observations on the presence or absence of xanthoma cells. Urbach's published list at once shows that the mere presence of xanthoma cells cannot be depended on for final classification.

In our case it is desirable to analyze the circumstances within the first as well as those within the second of these two larger fields because it is theoretically possible that, although our case as we observed it was one of a xanthelasmic condition it may not have been fundamentally so; that is, the xanthelasmic features may have been superimposed on a nonxanthelasmatosis as a secondary phenomenon incident to local excesses of lipid (resorption xanthelasma of Urbach). Thus, there may have been, theoretically, a fundamental lipoid proteinosis or an extracellular cholesterosis in which the excess of lipoid was such as to result in imbibition by such cells roundabout as were predisposed. Incidentally, it may be advisable to analyze all future cases of xanthelasmatosis in this light; indeed, they should be considered not alone in respect to an underlying nonxanthelasmatic lipoidosis but in respect to various dermatoses which are not at all lipoidal in nature (nevi, scars, erysipelas, lichen planus hypertrophicus, rheumatic nodules, tumors and zoster, i. e., the resorption xanthelasmas and xantheloids of Urbach). For example, is it possible that the lesions of some drug eruptions and of erythema multiforme serve as the predisposing foci for deposition of superabundant lipoids, whether locally or in connection with hyperlipoidemia, and then become "xanthomas" as one now knows them? In this light it is incumbent to compare with the condition in the case which Schaffer and I observed all the cutaneous lipoidoses listed by Urbach, because in them at least it is assured that a vice of lipoid metabolism existed.

I shall dispose of the simplest first: Gaucher's disease, Niemann-Pick's disease and hepatosplenomegalic skin and mucous membrane lipoidosis may be readily eliminated because in our patient there was no enlargement of either the spleen or the liver; both organs were definitely smaller than normal. Necrobiosis lipoidica diabeticorum

obviously had nothing in common with the condition described by Schaffer and me. It is unnecessary to go into details here.

Imbibitio lipoidica telae elasticae degeneratae (an elastosis) pertains to the skin; in our case an elastosis was met only in the internal tissues —in the larynx, aorta and retropharyngeal "tendon." Furthermore, however the processes in our case may (and only in part) have been of the pathologic order of those met in Urbach's "imbibition," they do not compare with it when the entire symptomatology is considered. All that could be claimed is that in connection with hyperlipoidosis, whether local (near a xanthomatous larynx) or in connection with hyperlipoidemia, certain of the elastic tissues imbibed lipoid. Certainly Urbach's complex, as he described it, may be dismissed from consideration in our case except in a minor, more or less incidental and secondary way.

In extracellular cholesterosis the distribution of lesions, the clinical course, the symptomatology and the prognosis are utterly different from those in our case. Apart from the xanthomatous aspects, the dermatosis suggested a local condition like hypertrophic lichen planus, at least dermatologically. Urbach's resorption xanthelasmas imply a local process radically different from such profound constitutional changes as resulted in the death of our patient.

Without calling on various other items which could be summoned, this sufficiently disposes of eight of the nine members of Urbach's list. There remains only xanthelasmatosis with which the condition in our case could be identified. Under this heading Urbach listed most of the types of "xanthoma" which are currently known as such to dermatologists. Of them, xanthoma planum, xanthoma tuberosum, "juvenile xanthoma and the *xanthome en tumeurs* of the French (xantheloid of Urbach) are obviously different from the condition in our case. Incidentally, he thought that there is no such thing as a genuine fundamentally neoplastic xanthoma. Cholesteroderma is a pseudo-icteric condition—so diffuse is the infiltration of the skin; it is easily rejected from consideration in this study. As to Hand-Christian's disease, the icterus, exophthalmos and involvement of the cranial bones were lacking in our case. Xanthoma hepaticum and xanthoma nephriticum need be but mentioned; Urbach stated that there are no distinctive dermatologic features in those conditions.

Special consideration, however, must be given to diffuse xanthoma and to xanthoma diabeticorum. The former is included by Urbach, as a special coalescent type, in xanthelasma planum and must be discussed here because the inflammatory areola and pigmentation which he stated occur in many cases of xanthoma planum in general were also present

in the case which Schaffer and I studied. Furthermore, Urbach cited the occurrence of xanthoma planum on the cheeks, neck, ear, lips and scalp and on the mucous membranes of the mouth, trachea, esophagus and bronchi. Indeed, he gave illustrations of nodular xanthomas of the ear associated with a plane xanthelasma covering almost the entire face. This is an unusual idea of the scope of xanthoma planum as currently understood in the United States. It appears to be based on morphology instead of on associated circumstances (hypercholesteremia and the subdiabetic state) which might remove such extra-ocular involvement from the well established (periocular) entity xanthelasma planum. In any event, whereas in our case there were palpebral lesions (they were nodular, too) there were also such extensive lesions around the anus, scrotum and elsewhere as to remove any possibility of the condition belonging to the entity xanthoma planum.

Xanthoma diabeticorum merits more detailed discussion in view of the designation "pseudodiabetic" proposed by Schaffer and me for the entity which we described. Data will be arranged in form appropriate for differential diagnosis. Common to the condition reported by us and to that described by Urbach were marked emaciation (with an apple-like odor of the breath, connoting the acidosis of cachexia), intolerance for dextrose and the definitely "inflammatory" and pigmentary type of the eruption. The records are not clear as to polyuria, polydipsia and polyphagia; they were probably absent. The patient stated that he micturated frequently, but the total quantity of urine passed was not excessive. Against the diagnosis of diabetes mellitus were the absence of glycosuria and hyperglycemia and certain features of the dermatosis. Thus, the furious (usual) itching was absent, the palms exhibited no linear xanthomatous streaks, the development of lesions was not abrupt, the lesions did not regress as a result of insulin therapy and the laryngeal involvement would probably be found to be unique for genuine diabetic xanthoma. Above all, the mode of development distinguishes pseudodiabetic xanthoma not alone from the diabetic form but from all the forms recounted among the lipoid disturbances of the skin cited by Urbach. Thus, the xanthic features were superimposed in part (early stages) on a diffuse erythema of the face and in part (later stage) on scaly foci (parapsoriasis) of the trunk and upper extremities, whereas lesions of diabetic xanthoma are definitely so localized that they are often reminiscent of pustules in the beginning.

The pseudodiabetic xanthoma which we described, then, cannot be reconciled with any of Urbach's forms on the basis of clinical features. Considering next the situation from the histologic side, lipoid proteinosis can be at once excluded because its smooth hyaloid characters (colloid-like) were not met in our sections. Imbibitio lipoidica telae elasticae

degeneratae deserves consideration, however, in view of the striking lesion posterior to the larynx; its yellow color on gross examination and the histologic appearance class it in that category. However, the sections have been reexamined, and it can now be stated that similar changes were not observed in the skin. Hepatosplenomegalic skin and mucous membrane lipoidosis can be dismissed on the same basis. In intercellular cholesterosis a certain complication is possible because lipoids in xanthelasmas may be also found in part intercellularly, but the association of foam cells would decide the diagnosis in such cases. It would be advisable to lean heavily on the clinical observations under such circumstances. Fortunately, however, there were not any intercellular deposits in the case which Schaffer and I observed. Gaucher's disease would be readily distinguished by its distinctive type of foam cell if it were ever met in the skin; the cytoplasmic network is coarse indeed. Necrobiosis lipoidica diabeticorum can be eliminated because there were in our sections no necrobiotic foci from which the lipoid material could have been resorbed. In any event, all the previously mentioned diseases are eliminated from consideration because in them foam cells are not present.

However, it is conceivable that such cells might be seen in the skin in Niemann-Pick's disease, but thus far the skin has apparently not been reported as being involved in that extremely rare disease. There thus remain only the xanthelasmas and resorption xanthelasmas to consider further, since foam cells are a feature in these two groups. As to the latter, there were not any recognizable local foci of lipoidal change in our sections which could serve as sources from which resorption could take place. Here again, then, the disease in our case can be placed only among the xanthelasmas. This was also the conclusion reached when the circumstances were analyzed from the purely clinical angle.

From the standpoint of histochemistry, as already stated, the results of our studies were not satisfactory in respect to the lipoid fractions. It appears, though, on the basis of morphology and of behavior toward sudan III, that neutral fat and cholesterol were but minor constituents or were perhaps absent. Apparently, fatty acid crystals constituted the bulk of the lipoids, but they stained deep red with sudan III in a way that is inconsistent with the reaction of fatty acids, and as a result of pressure of the cover slip fused into large globules which stained deep red and were identical in appearance with neutral fat. It is quite conceivable that in a case like ours, in which the observations were unusual in so many respects, the composition of the lipoids in the lesions was also unusual. Incidentally, tests of chemically pure tristerol and tripalmitol crystals with sudan III and other stains, both in test tubes and in frozen sections, did not result in the reactions which are claimed by

many authors. Some sources of error in connection with studies of mixtures of lipoids are discussed at length elsewhere.[4]

To summarize, it is proposed that pseudodiabetic xanthoma which Schaffer and I [1] described be placed among the xanthelasmas of Urbach. It cannot be reconciled with any of the forms which he has described, even when one omits such formidable features as the gastric cancer and the lesion of the pons and cord which were present in our case. It should occupy a position adjoining, but not related to, the "special type of generalized, outstandingly internal xanthelasmas" with which Urbach classified Hand-Christian's disease. Only the study of future cases can illuminate the question whether the "tumor" of the pons played a rôle in this pseudodiabetic xanthoma analogous to that of the pineal and pituitary involvement observed in Hand-Christian's disease.

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4. Weidman, F .D.: Xanthosarcoma of the Cheek Succeeding Xanthosarcoma of the Forearm: Multiple Tumors Versus Metastasis, Arch. Surg. **34**:792 (May) 1937.

TREATMENT OF EPITHELIOMA OF THE LIP BY ELECTRODESICCATION

TECHNIC AND PRELIMINARY REPORT OF RESULTS DURING THE PAST FIVE YEARS

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AND

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The treatment of epithelioma of the lip is considered by most physicians to be strictly a surgical problem. In some of the standard textbooks on dermatology the only treatment advised is surgical excision of the primary growth and associated lymph nodes. The purpose of this paper is to describe a technic for the treatment of early stages of epithelioma of the lip which can be readily carried out on ambulatory patients in the dispensary or in the private office of the dermatologist.

PRINCIPLES OF TREATMENT

In the treatment of malignant disease the essential factor is the complete destruction or removal of all neoplastic cells. It is desirable that this be accomplished with as little damage to normal tissue as possible to preserve the function of the region involved and to produce the best cosmetic result. A minimum loss of time from work is also of importance. There are three recognized methods used in the treatment of malignant neoplasms, i. e., surgical therapy, irradiation and cautery. Various combinations of these basic methods are also utilized.

Surgical Therapy.—This method, if properly performed, results in a high percentage of cures. It is important to note that epithelioma of the lip has a tendency to extend laterally under the mucous membrane. The deep involvement is considerably wider than appears on the surface. For this reason the classic V excision of these lesions has given place in most clinics to a modified H or U operation. The majority of surgeons formerly believed that a radical dissection of associated lymphatic chains was essential in every case. In recent years several outstanding surgeons have pointed out that in 80 per cent of the cases

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of epithelioma of the lip metastases do not develop early. The chief objections to surgical therapy are the loss of considerable normal tissue and the fact that in most instances the operation is performed in a hospital, which adds to the expense and intimidates the patient.

Irradiation.—During the past thirty-five years irradiation of cancer generally and of cutaneous cancer in particular has been recognized as an important method of treatment. Adequate irradiation is capable of curing a large percentage of epitheliomas of the lip. It is of outstanding value in the palliative treatment of the inoperable and extensive lesions occasionally encountered. There is little difference between radium and roentgen irradiation except that in cases of massive involvement the use of interstitial treatment by means of radium element needles or radon seeds is of considerable value. The chief shortcoming of radiation treatment of cancer of the lip is the fact that the resulting scar may, in the course of time, exhibit the usual after-effects of intensive radiation, such as atrophy, telangiectasia or keratosis. The damage done to adjacent normal tissue, though it may not be apparent, increases the difficulty of treating a recurrence or a new malignant growth in the same area. The lack of material for microscopic examination and the fact that the lesion remains from two to four weeks longer than in the case of other methods are further objections.

Cautery.—The destruction of neoplasms by cautery is also effective if thoroughly done. This may be accomplished by means of a hot iron, chemical cauterization or electrothermal destruction. In the modern electrodesiccation or electrocoagulation apparatus the heat is produced in the tissues by means of a monopolar or biopolar alternating current of high frequency. This current may be so modified as to produce the so-called cutting current in which the current divides and sears the tissue as the instrument passes through. All these cauterizing methods are open to the objection that in order to be certain of destroying all the malignant tissue one must sacrifice a considerable amount of normal tissue.

Combination of Methods.—Various combinations of these methods have been suggested and have met with a considerable degree of success. Surgical treatment combined with irradiation is perhaps the most frequently employed. This is particularly practiced in the so-called prophylactic irradiation of the cervical areas after the removal of the primary growth. For many years dermatologists have employed thorough curettage followed by some form of cauterization or by irradiation in the treatment of cutaneous new growths. Until recently this method has been reserved for lesions of the glabrous skin, but gradually it has also become a recognized form of treatment for epithelioma of the lip.

CURETTAGE AND DESICCATION

For the past five years we have regularly treated epithelioma of the lip by means of curettage followed by electrodesiccation.

Method.—The procedure is readily carried out in the office or in the dispensary. The area is anesthetized by injecting 1 or 2 cc. of a 2 per cent solution of procaine hydrochloride around the lesion. The lip is compressed between the thumb and forefinger by an assistant, and the pulpy tissue is removed by means of a sharp curet. This permits a far more accurate survey of the extent of the lesion than can be obtained by inspection and palpation. In most instances there is little or no bleeding. A piece of tissue for microscopic examination may be removed with a biopsy punch before curetting is started, or the curetted material may be saved for this purpose. The growth frequently shells out, showing a line of demarcation between it and the normal tissue. After curettage, the area is treated with a rather intense monopolar current, the tissue being desiccated to a depth of 2 or 3 mm. The lesion is dusted over with an antiseptic powder once or twice a day. A dressing is rarely required. In the course of ten days or two weeks the slough separates, and the area heals in about six weeks. Ordinarily, the patient is able to continue with his occupation. The resulting scar is frequently thick at first, but in the course of a few months it usually flattens out, leaving a surprisingly insignificant slightly indurated area.

Complications.—The one complication which is encountered in about 1 of 12 cases is hemorrhage. This occurs as a rule at the time the slough separates. It is generally not severe and is readily controlled by compressing the lip for a few minutes between two fingers. Occasionally a suture or tie is required, and usually this is used to quiet the nervousness of the patient and his family rather than because of necessity. A solution of ferric subsulfate or silver nitrate is at times useful in controlling the bleeding. There is no apparent connection between the extent of the lesion or the intensity of the desiccating spark and the occurrence of hemorrhage. It is conceivable that secondary infection may be a complication of this type of treatment, but so far we have not seen any marked degree of infection, though it is not unusual to find a few drops of pus under the eschar about two weeks after treatment. If this is present, the crust is removed and the floor of the ulcer is gently sponged and dressed for a day or two with a mild antiseptic ointment such as 2 per cent ammoniated mercury in zinc oxide ointment and then the antiseptic powder is again applied.

Comment.—The treatment which has been outlined is particularly adapted to early lesions which have not penetrated the muscle. It is often impossible to gage the extent of the neoplasm until after curettage has been started. Long-standing lesions with palpable metastatic masses

in the cervical lymph nodes are referred to the surgical or to the roentgenologic department. Instances of keratotic lesions of the lip which are only suspected of having undergone malignant degeneration are treated as if they were early stages of epithelioma.

The treatment of the adjacent lymphatic chains is a point about which there is much disagreement. Many surgeons still believe that a gland dissection should be performed in every case of well developed cancer. Statistics have shown that metastases develop in only about 20 per cent of the cases of apparently localized cancer. When lymph nodes are palpable, operation frequently shows that they are not the seat of malignant changes. Most surgeons now believe that gland dissection is indicated only in the presence of palpable lymph nodes. The routine irradiation of the cervical region in the absence of palpable nodes as a prophylactic measure is of doubtful value.

It may be argued that radium or roentgen irradiation of the lip after desiccation should be valuable in preventing recurrence and in decreasing the likelihood of the formation of a thick scar. The scar has not been sufficiently marked in the majority of instances to merit the additional expense and time required for irradiation. The introduction of irradiation would lead to the possible late results mentioned in discussing the shortcomings of this form of treatment, and there is no evidence that it would materially decrease the number of recurrences.

STATISTICS

In reviewing the case histories of the patients with epithelioma of the lip whom we have treated by curettage and desiccation, we were disappointed to find that 23 of 54 patients treated in the clinic and 31 of 85 of those treated at the office could not be traced. This is due to the lack of an adequate follow-up system in both the office and the dispensary. Of the 54 patients treated at the office from whom data as to the end-results were obtained, 43 were well and had no evidence of disease from six months to five years after treatment. Of the 26 patients treated at the clinic who were traced, 23 were apparently cured. These figures represent data on patients whom we have seen recently or who answered a request for a note as to the present condition of their lips. Table 1 shows the results as far as we were able to check them. A number of the patients classified as "well" have had recurrences which responded to the same form of treatment. Others have had new carcinomas on a different portion of the lip. It is often difficult to decide whether these are recurrences or really new neoplasms. The patient listed as having been cured elsewhere had had two apparently different epitheliomas removed by us. When a recurrence or another new lesion developed, he went elsewhere, and according to

his record has remained well since. The 2 patients listed as having died of cancer of the lip both had indurated rather extensive lesions extending onto the inner surface of the lip and the buccal mucosa. We no longer treat lesions of this type by desiccation. In all patients who died of other causes the lesions on the lip had not recurred. Under the heading of "not cured" are placed 1 patient who reported that there might be some remaining activity and 2 with recurrences which have been recently treated. In table 2 the patients listed as well are classified as to the time that has elapsed since the last treatment. It seemed to us that the number of patients followed is too small to justify a more extensive statistical review.

TABLE 1.—*Statistical Summary of Data on Patients Treated by Electrodesiccation*

Results	Number of Patients Treated in the Office	Number of Clinic Patients	Total
Well	43	23	66
Cured elsewhere	1	0	1
Dead of cancer of the lip	2	0	2
Dead of other causes	6	2	8
Not cured	2	1	3
Traced	54	26	80
Not traced	31	28	59
	85	54	139

TABLE 2.—*Duration of Clinical Cure to Date*

Number of Patients Cured	Under 1 year	1 to 2 years	2 to 3 years	3 to 4 years	4 to 5 years
Treated in the office	8	14	9	8	4
Treated at the clinic	11	5	2	2	3
Total	19	19	11	10	7

In every instance of epithelioma of the lip here recorded we have examined sections of the material microscopically. It is probable that some sort of classification according to microscopic appearance, such as that devised by Broders, may be of prognostic value. We have, however, made no attempt to grade the lesions by such a method because we have felt that it served no practical purpose, especially in consideration of the fact that our sections dealt in most instances with only a small portion of the growth.

Wile and Hand in their paper presented at the meeting of the American Medical Association a few weeks ago expressed the opinion that the results in their cases were excellent with either surgical removal or local destruction. For economic reasons they preferred local destruction in cases of early lesions. They did not advise roentgen therapy or resection of glands in cases of early or moderately advanced epithelioma.

SUMMARY

During the past five years we have treated 139 patients with early epitheliomas of the lip by curettage and electrodesiccation, the site being under local anesthesia, in the office and in the outpatient department. The clinical and cosmetic results are apparently as good as those which follow surgical therapy. This method of treatment is recommended on the basis of its effectiveness, of the ease with which it can be applied and of its small expense to the patient.

ABSTRACT OF DISCUSSION

Dr. Clark W. Finnerud, Chicago: Until about two years ago I had always considered cancer of the lip purely a problem for the surgeon. Dr. Morrow, when passing through Chicago at that time, explained his technic to me and spoke of the good results obtained, and since then I have had occasion to use the method in several cases of selected carcinoma of the lip. Although the time is rather short, only two years, the results have been uniformly good. I have not yet observed recurrences such as were mentioned in the paper. I have also used rather deep electrocoagulation in some instances, and in those cases I have had a good deal of worry over a period of several months, until I was able to decide that the palpable deep nodule which is usually felt between the mucous membrane and the skin was probably deep scar tissue resulting from coagulation. In each instance this has later become entirely absorbed. Such a nodule does not follow curettage and desiccation as the authors use the methods, but in place of it there is a soft scar causing practically no appreciable deformity.

It is known that about 100 per cent of all carcinomas of the lip are of squamous cell type. They differ only in grade, and the treatment employed must be thoroughly destructive, whether it is purely surgical or consists of other procedure.

I believe this is a field in which dermatologists are justified in treating selected lesions, and I think that this paper demonstrates this fact.

Dr. David L. Satenstein, New York: A number of years ago I was impressed by the following things: I saw a patient with a rather superficial epithelioma of the lip associated with some keratinization or plugging on other portions of the lip. In cases in which the neoplasm was thoroughly destroyed and the leukoplakic or keratotic area was destroyed patients have come back after several years because of a recurrence in the leukoplakic area which had been slightly desiccated. I suggested to Dr. Eller, with Dr. MacKee's permission, that when a leukoplakic area was present the entire vermilion border of the lip should be desiccated. The lesions were thoroughly studied histologically, and in every case I observed atypical cells developing in the leukoplakic or keratotic area. In cases in which the epithelioma of the lip was intra-epidermal, that is, had not broken through the epithelial layer, we found that no further therapy was indicated. In the cases in which the neoplasm had broken through the basal cell layer and had begun to involve the area about it the patients were always referred for radiation therapy, and whether the lesion was palpable or not they always received radiation. In cases in which there was infiltration in the lymph nodes the patients were given further therapy.

I have never found examination of curetted material satisfactory. I could not get an accurate picture of what was taking place. I have never hesitated to

take out a section, for a report can be obtained in three or four days, or within a few minutes if a frozen section is made.

I believe that when there is a keratosis on other portions of the lip the entire vermilion border should be removed. The cosmetic result is splendid. In cases in which this is done the lip may be drawn up, but soon it begins to granulate in, and within a few years one can hardly tell that anything has been done. The only difficulty encountered in removing the entire vermilion border was cutting into the arteries. In those cases Dr. Eller tied off the arteries. My co-workers and I use the cautery or the high tension knife. I think searing the lymphatics is unnecessary. There is no negative pressure, and nothing will be sucked into the lymphatics when they are cut open; any cells that come off on the knife will die anyway. The problem is different in cases of carcinoma of the breast, in which a piece of tissue is taken out and the wound is then sutured, but on the lip I think it makes no difference whether the actual cautery or the spark knife is used. I prefer the actual knife, for it permits the operator to see what he is doing, whereas the spark knife may go deeper than one intended it to go.

Dr. Joseph A. Elliott, Charlotte, N. C.: I am much interested in this presentation, for I have been treating epitheliomas of the lip by a similar method for the past fifteen years.

My method differs slightly from that of Dr. Morrow and his associates. I, like Dr. Satenstein, am unable to obtain a satisfactory biopsy specimen with a curet, and therefore I employ a small cutaneous punch. After the specimen is obtained, the entire lesion is curetted and the base is thoroughly desiccated. All my patients receive roentgen therapy to the local lesion, and those with extensive lesions as well as those showing a high degree of malignant degeneration microscopically receive high voltage roentgen therapy to the adjacent glands.

Thus far I have had no local recurrences and only one metastasis. The patient who had a metastasis did not receive roentgen therapy to the neck. It is my opinion that desiccation, plus irradiation, offers the best method of treating early epithelioma of the lip.

Dr. Howard Morrow, San Francisco: One object in bringing up this subject was to stimulate dermatologists to treat epithelioma of the lip, because the results which my co-workers and I obtained were so satisfactory and the general impression was that is was necessary to refer all patients with carcinoma of the lip to the surgeon. For five years we have treated all such lesions with desiccation. We do not use irradiation before or afterward. We feel that when the lip has been properly treated by desiccation there is no need for irradiation, for there will be no recurrence if the glands are not involved.

There are two points I wish to emphasize. One is courage. I think one should curet the lesions with a good deal of friction. One cannot curet away healthy normal tissue, and we use a great deal of pressure in attempting to remove all of the diseased tissue. This is followed by desiccation, pressure being applied on the lip, and there is little bleeding. But, as was mentioned, there may be bleeding afterward, and when this occurs it is usually in the middle of the night, or at 3 or 4 a. m. We tell the patients that the lesions may bleed and that if they do the lip should be held firmly with the fingers for five minutes.

Dr. H. E. Michelson, Minneapolis: I am aware that in listening to this paper the association does not necessarily subscribe to the method as one of choice, but all the members realize that it is one of the ways of handling cancer. I wonder what the effect of a paper of this sort would be if the listeners were a group of cancer specialists. As a member of a group of cancer specialists I

want to stress the approach to the treatment of cancer of the skin more than the selection of a single method. In our institute my co-workers and I are more concerned with the selection of the proper treatment in the particular case, and we feel that many different treatments for cancer are entirely sound if properly carried out. We consider the following points: the age of the patient, the anatomic location, the morphologic characteristics, the size of the lesion, its duration, the state of growth and the previous treatment. In cases of cancer of the lip and mouth we pay particular attention to the oral hygiene. I believe that a microscopic evaluation is the correct method of determining the proper treatment, but it must be interpreted, not by the pathologist removed from the patient, but by the physician who considers both the microscopic picture and the other points about the growth. For example, a basal cell cancer may be given a good prognosis by a pathologist but because of its extent and location well may have a poor prognosis in the opinion of the clinician. Therefore, I think it is necessary to consider both the patient and the growth before subscribing to a certain form of therapy as that of choice.

Dr. Eugene F. Traub, New York: My co-workers and I have been attempting the treatment of these lesions for a number of years, and I do not believe that the method of local management, while important, is the most essential consideration. It seems to me that the most important points are the determination of the type or grade of carcinoma present and the selection of the patients, particularly with the thought of metastasis in mind. It has been definitely brought out that there is nothing about the appearance, duration or extent of a local lesion that gives any clue as to the question of metastasis. The paper of Dr. Robert H. Kennedy (*Ann. Surg.* **99**:81-93 [Jan.] 1934) covers all these points by means of accurate statistics presented in a remarkably interesting manner. He observed that in many instances early lesions had metastasized even though palpable nodes were not to be found, and in other cases lesions of the lip of long standing associated with palpable nodes were proved on node dissection not to have metastasized, the nodes that were felt being simply inflammatory. Another important point is that it is at times difficult, even for an expert, to be certain that the lesion on the lip is actually an epithelioma and not simply a verrucous or benign lesion. It is obvious, of course, that benign lesions, mistaken for cancer of the lip, would swell out of proportion favorable statistics if the diagnosis is not properly controlled by a careful microscopic examination. Recently in association with a cancer surgeon I observed 2 cases which illustrate the point I am trying to make. In 1 the patient had a lesion of the lip of two years' duration which had previously been removed and had recurred, and on wide surgical excision this lesion proved to be nothing more than a wart. In the second case, in which the lesion was presumably of less than four weeks' duration, it proved to be an early carcinoma despite a rather innocent clinical appearance. The value of making a histologic examination, therefore, cannot be overemphasized.

Regarding the method of local removal, much can be said for a large number of procedures. However, I believe that it requires great experience to be able to curet a carcinoma of the lip and be certain to have gone beyond any possible extension. No doubt those who have had a great deal of experience can tell by the sense of feel as well as by the appearance when they are in safe ground, but for the majority of men to attempt such a removal, I think is exceedingly unwise. A much safer method is to remove the local lesion by means of the electric cutting current and so mark the removed specimen that the pathologist can tell immediately if any border was not sufficiently widely removed. This is a perfect check on the operator and an added safeguard to the patient.

Adding to the local treatment radiation therapy either before or after is, as the authors have stated, entirely unnecessary provided the lesion has been thoroughly removed. The irradiation only adds to the hazard of the procedure, and I believe it is generally conceded that little is to be gained. Roentgentherapy to the nodes of the neck as a prophylactic procedure also seems valueless, and my co-workers and I have discontinued the practice.

Dermatologists should realize, as Dr. Michelson has stated, that they are more or less "on the spot" when treating metastatic carcinoma. There is no doubt that one can treat many of these lesions successfully, possibly as high a percentage as 80, because of the lack of metastasis, and, of course, in most cases in which such results are obtained the dermatologists' work will not be criticized; but if in 1 case metastases do occur and the patient must be referred to a surgeon later, that does not add to the dermatologist's reputation.

Dr. J. H. Blaisdell, Boston: The thought of dermatologists treating cancer of the lip is heresy to the surgeons. I do not go as far as that by any means, but I am glad to refer to a surgeon patients with involvement of the mucous membrane and those with palpable glands. Cancer of the surface of the lip can be treated by dermatologists, and I think that the method that involves least trauma to the tissue is the best. For that reason treatment with radium, which is selective and not traumatizing, is the method of election. I do not think that the possibility of radiodermatitis developing years later is particularly important. If a patient with cancer of the lip who is 60 or 70 years old lives long enough to have radiodermatitis fifteen years later he is fortunate.

Dr. Louis A. Brunsting, Rochester, Minn.: I believe the points mentioned by Dr. Elliott and Dr. Michelson are exceedingly well taken. There is a marked variation in patients as regards susceptibility to cancer, and Broders proved that the degree of activity of the malignant process is a good index to prognosis. In cases of squamous cell epithelioma of grade 1 in which epithelial pearls are abundant, the cells are still well differentiated, mitotic figures are few and the prognosis is good. On the other hand, in lesions classified as grades 3 and 4, in which the cells have lost their differentiation and mitotic figures are abundant, there is frequent involvement of the adjacent lymph glands early in the disease and the prognosis is correspondingly poor. In this group the percentage of cures is lowest regardless of the method of treatment. As a rule in cases of more active involvement I advise removal of the adjacent lymphatic chains and possibly some form of radiation therapy in addition to complete removal of the primary lesion.

Dr. Fred D. Weidman, Philadelphia: The proof of the pudding is in the eating and not in chewing the string. The tables speak for themselves—there can be no question but that the results were good. There is one point, though, which I wish to bring up. When I was on the Pacific Coast I saw Dr. Miller remove one of these lesions and was amazed at the ease with which the lesion shelled out. Later, some one told me that many of the carcinomas observed in California result from the actinic light of the well known California sunshine, the dry hot winds and alkali dust. Possibly this plays a rôle in determining a particular type of carcinoma. That may explain why it is that in the locality in which the material for this paper was gathered such excellent results are obtained. Since I observed only 1 case, I should like to know whether there is a large percentage of such cases included in the study.

Dr. Harold N. Cole, Cleveland: I subscribe to the view of Dr. Michelson. I think that as a rule the results are better if the therapy with endothermy is

limited to the lesion that involves only the cutaneous portion. If the lesion is large enough for removal to cause much scar tissue, it is better to use radium needles.

In treating these lesions my co-workers and I have used the method recommended by Pfahler. We have treated a large number of lesions, and in spite of the fact that we do not have hot winds and alkali dust in Ohio I think there is not much difference in type. We add a small amount of epinephrine to the procaine hydrochloride to keep the region free from blood. We are thereby enabled to get a better idea of the pockets. We desiccate before we curet. This seems to fuse the tissues and makes it possible to find all the little pockets. We follow this up with endothermy. Repeated desiccations and curettage make it possible to find all the foci that cause trouble.

I think a biopsy should always be made. Patients with the squamous cell type of lesion certainly should receive radiation to the lymph nodes. If there is any question of extension at all these patients should probably undergo dissection of the lymph nodes as well. I do not think, however, that this is necessary in cases of small lesions of the lip. In cases such as those referred to by the authors I believe that the procedure described is the treatment of choice, and I think this is a timely paper.

DR. LAURENCE R. TAUSSIG: The discussion has been so extensive that it is manifestly impossible to speak about all the questions brought up.

I think any well trained dermatologist will rarely make a mistake in diagnosing carcinoma of the lip. Perhaps I am unduly optimistic, but I do not think that one is likely to diagnose as carcinoma of the lip a wart or a pyogenic lesion.

In the matter of the thickened scar of which Dr. Finnerud spoke, my co-workers and I also were rather nervous about the thick scar which develops after the lesion heals, but in practically every case it has flattened out in the course of a few months or of a year or two, and a good cosmetic result has been attained.

I wish to say a few words about radiation therapy in cases of carcinoma of the lip. We have had an emanation plant for fifteen years. Before that we had a supply of radium and treated a number of carcinomas of the lip. We have observed many patients in whom new lesions developed on other portions of the lip six or seven years after treatment, and there is no question but that radiodermatitis increases the difficulty of treating such lesions.

I do not believe that carcinoma in California is different from that elsewhere. I think that a large number of these lesions shell out, as Dr. Wiedman mentioned, but they do not all do so. We think that in the blonde type of man with sandy complexion who works in sun and wind, whether it is in California, Texas or New York, carcinoma frequently develops.

Perhaps we did not stress sufficiently the matter of selection of cases. We have felt that this type of therapy is particularly adaptable to early lesions, and we have been fortunate in seeing many of these early lesions.

In regard to Broders' classification, which was touched on in the paper, we have gathered the impression that the clinicians have accepted Broders' system of classification rather wholeheartedly, but in talking to pathologists we found that considerable skepticism was expressed as to the value of such a classification.

PURPURA

CLASSIFICATION AND TREATMENT, WITH SPECIAL REFERENCE TO TREATMENT WITH SNAKE VENOM

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This paper is an attempt to place before dermatologists an analysis of the purpuric and allied manifestations of the skin and mucous membranes. This analysis will include a classification of purpura from dermatologic and hematologic standpoints. A brief description of the comparative histology is given. In addition, the use of venom as an aid in the diagnosis, classification and prognosis as well as in treatment of these conditions is proposed.

BASIC ELEMENTS OF PURPURIC MANIFESTATIONS

Purpura is essentially a hemorrhage into the skin or mucous membranes. The various terms employed, such as petechiae, ecchymoses, purpura, hematoma, black and blue spots, vibex and suffusion, are quantitative and qualitative descriptions of this hemorrhage. The definition of these terms as they are understood in our presentation is as follows:

1. Petechiae: Minute hemorrhages from the size of a pinpoint to that of a pinhead in the skin or mucous membranes.

2. Ecchymosis (black and blue spot): Purplish spot resulting from hemorrhage up to palm size.

3. Purpuric lesions: Synonymous with either petechiae or ecchymosis.

4. Hematoma: Collection of effused blood resulting in tumor formation.

5. Vibex: Linear ecchymosis.

6. Suffusion: Large extravasation of blood without evident tumor formation.

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COLOR OF PURPURIC LESIONS

It is surprising to find a paucity of experimental data to explain the color of the various purpuric manifestations. Petechiae, whether appearing spontaneously or after the application of a tourniquet test or of suction, are always red. Ecchymotic lesions are usually blue. The few textbooks that discuss the cause of the different colors in such lesions either offer no explanation or make the statement that fresh lesions are red and that the older lesions are blue.

We have performed a few simple experiments which when coupled with some of the histologic observations cited clearly explain the color of purpuric lesions. A 10 per cent solution of hemoglobin in sterile physiologic solution of sodium chloride was prepared. One-tenth cubic centimeter of this solution was injected intradermally. There resulted a small bluish black wheal. Seventy-two hours later the site of injection had become a decided reddish blue. When the same solution of hemoglobin was injected deeper under the epidermis the site remained blue. Blood was then taken from the median cephalic vein of the patient on whom these tests had been made and immediately reinjected subcutaneously and intradermally in amounts of 0.2 and 0.5 cc. According to the amount of blood injected, the area varied from a light to a deep blue. Seventy-two hours later this area was still bluish black.

Petechiae, whether produced by trauma or appearing spontaneously, showed on histologic examination dilated small vessels, usually capillaries, right under the epidermis and in the upper and middle layers of the cutis, with only a relatively small amount of free hemorrhage in the surrounding tissues. The dilated vessels were filled with blood. Small spider nevi and small angiomatous lesions as well as telangiectases were also always red. Histologic examination of such lesions, unless there was an accompanying inflammation, showed no hemorrhage in the tissues, and the engorged and dilated small vessels were seen to be situated immediately below the epidermis. The large flat vascular nevi had a purplish color and showed on microscopic examination large, dilated vessels engorged with blood in the deeper portion of the cutis. Purpuric lesions, blue in color, produced by the injection of endothelial toxins such as snake venom presented on histologic examination a fairly large amount of hemorrhage in the middle and lower portions of the cutis.

We deduced from these observations that the red color of petechiae was due to the presence of small dilated vessels filled with blood and of a small amount of hemorrhage immediately below the epidermis or in the upper layers of the cutis. When there were large dilated vessels filled with blood and enough free hemorrhage in the middle and lower layers of the cutis, there was invariably a bluish lesion. This applied as

well to the presence of free hemoglobin in the tissues. It also explained the change from blue to red of the injected solution of hemoglobin. The absorption of the hemoglobin was greatest in the deeper parts of the cutis, and the decreased amount of this substance right below the epidermis gave a red reflex. With the breakdown of the hemoglobin to hemosiderin the familiar play of colors from blue to green to yellow took place.

THE ANATOMY OF THE BLOOD SUPPLY OF THE HUMAN SKIN [1]

The skin is supplied from the underlying tissues through small arteries. In the deepest portion of the cutis the arteries form a rich anastomosing plexus from which small arteries rise perpendicularly through the cutis to form, below the papillae, a subpapillary plexus. From this still smaller arteries spring to supply the papillary capillaries. These do not anastomose, but each supplies a small but variable number of papillae. Each papilla is normally supplied by a central capillary loop the arterial branch of which is narrow and widens toward the tip of the loop to the subsequent venous branch which may be 0.02 mm. or more in diameter. The venous branches of the papillary capillaries then continue to form venules which return first to a subpapillary plexus of veins. These are connected by short anastomoses with a second venous plexus which lies at the arterial subpapillary veins. Between the cutis and the subcutis valves appear in the veins. No valves are seen in the venules of the cutis.

There is no sharp distinction between the smallest capillary arteries,[1] the capillaries proper and the venules (capillary veins). Lewis [2] introduced the term "minute vessels" of the skin to distinguish the aforementioned vessels from the "strong arterioles" and the deep veins.

MECHANISM OF THE PRODUCTION OF PURPURA

Purpuric hemorrhages are the result of the blood escaping from the "minute vessels" of the skin. This occurs either by diapedesis of the red blood cells which force their way between the endothelial cells or by actual rhexsis of the walls. Diapedesis of red blood cells can be caused by increased intracapillary pressure (tourniquet test), by suction (Cutter and Johnson machine) or by a reduction of the intercellular material between the endothelial cells, as in cases of scurvy and perhaps of other avitaminoses. According to Cohnheim,[3] in the mechanism of

1. Spalteholz, W.: Blutgefässe der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol 1, pp. 379-433.

2. Lewis, Thomas: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

3. Cohnheim, cited by Krogh, August: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1929.

diapedesis the red blood cells can pass through the capillaries smoothly, as through a hole. In static capillaries the vessel wall may bulge in one or more places, and the red blood cells which were in varicosed dilatations may flow outside the capillary walls. The integrity of the walls is rapidly restored.

Rhexis, or rupture, of the vessel wall in which the whole wall is involved can be due to toxins (bacterial), heavy metals, snake venoms or trauma (including increased intracapillary pressure) causing degenerative or inflammatory changes in the vessels.

In the study of inflammatory or toxic processes it will be seen that the rhexis occurs by direct action on the vessel walls combined with an inflammatory exudate. This is seen clearly and is a differential point in distinguishing this process from rhexis due to trauma alone.

The platelets are important in both mechanisms. They serve as plugs in an attempt to stop hemorrhage either when there is a lack of cement substance or when there is an actual capillary rupture. An added contributing factor in the formation of the larger hematoma is the lack of a proper coagulating mechanism. This is best exemplified by the large hematoma seen in hemophilia.

PROCEDURES FOR STUDIES OF BLOOD AND CAPILLARIES

A. CAPILLARIES.—The most common test for capillary fragility is the tourniquet test or Rumpel-Leede phenomenon. In carrying out this procedure a piece of soft rubber tubing is placed around the arm tightly enough to retard the venous flow. This is left on for from five to fifteen minutes. The number of petechiae which develop below or under the tourniquet is a gage of the capillary resistance to increased intracapillary pressure and indirectly tests the fragility of these small vessels. This method has many disadvantages, such as the difficulty of standardization and quantitative estimation. The test cannot be made at frequent intervals on the same arm, since the widespread petechial hemorrhage must be absorbed before the test can be repeated. In an attempt to make this method more accurate Göthlin [4] has modified the technic by controlling more accurately the amount of pressure expressed in terms of millimeters of mercury which is applied to the arm.

More recently suction has been applied to the capillaries as a gage of their resistance to negative pressure.[5] The apparatus which was

4. Göthlin, G. F.: Outline of a Method for the Determination of the Strength of the Skin Capillaries and the Indirect Estimation of Individual Vitamin C Standard, J. Lab. & Clin. Med. **18**:484, 1933.

5. Cutter, I. S., and Johnson, C. A.: Studies on Capillary Fragility: A Device for the Study of Capillary Hemorrhage, J. A. M. A. **105**:505 (Aug. 17) 1935.

described is rather complicated and expensive. The flicker or pinch tests are rather crude attempts to gage capillary resistance by direct trauma.

The Intradermal Venom Test.—The use of intradermal injections of venom containing endothelial poisons is a new approach to the study of capillary fragility.[6] This is based on the fact that certain venoms contain endothelial toxins, which have been named hemorrhagins. When these are introduced into the skin under proper conditions an ecchymosis results. Moccasin venom is a good source of hemorrhagins and is relatively low in other toxic properties.

The dried scales of moccasin venom were dissolved in physiologic solution of sodium chloride, and merthiolate was added as a preservative. The hemorrhagin content of the venom solution was titrated by means of the 4 day old chicken embryo,[7] a preparation consisting essentially of a heart and blood vessels. The amount of hemorrhage was determined by direct application of a solution of venom to this preparation. When the proper concentration was used petechiae developed along the vascular tree of the embryo. The venom was so titrated that 0.1 cc. of the solution of venom contained 1 unit of hemorrhagin. This was usually a 1:3,000 solution of the dried moccasin venom.

The intradermal venom test was carried out by the injection of 1 or 2 units of hemorrhagin (0.1 or 0.2 cc.), and the reaction was read after one hour or less. A similar quantity of physiologic solution of sodium chloride plus merthiolate was injected at the same time as a control. A positive reaction consists of a definite hemorrhage 1 cm. or more in diameter appearing at the site of injection. The color of the positive reaction is blue and occasionally a deep red, depending on the depth and amount of the hemorrhage. A delayed positive reaction shows a diffuse ecchymosis in from twelve to twenty-four hours. In the comment on the use of the test only the reaction seen in one hour has been evaluated (fig. 1).

The venom test has many advantages. It is simple; it is inexpensive, and because of the small area involved it can be repeated at frequent intervals. It is both quantitative and qualitative. The fragility of the capillaries can be tested in inacessible areas such as the mucous membranes, cheeks and center and periphery of cutaneous lesions. The hemorrhages following the introduction of the venom are due to dissolution of vascular continuity by the direct action of the endothelial poison. Diapedesis does not play a rôle as in the tourniquet or in the suction test.

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6. (*a*) Peck, S. M., and Sobotka, H.: Production of Refractory State as Concerns the Shwartzman Phenomenon by the Injections of Venom of the Moccasin Snake (Ancistrodon Piscivorus), J. Exper. Med. **54**:407, 1931. (*b*) Peck, S. M.; Rosenthal, N., and Erf, L.: Value of Prognostic Venom Reaction in Thrombocytic Purpura, J. A. M. A. **106**:1783 (May 23) 1936; (*c*) Observations on an Intradermal Venom Reaction, Proc. Soc. Exper. Biol. & Med. **35**:614, 1937.

7. Witebsky, E.; Peck, S. M., and Neter, E.: Demonstration of Hemorrhagins in Snake Venoms by Means of the Chicken Embryo, Proc. Soc. Exper. Biol. & Med. **32**:722, 1935.

B. Studies of the Blood.—Determination of the amount of hemoglobin, of the number of red and of white cells, of the differential count and of the number of platelets and study of the morphology of these cells are important in the classification of purpuric eruptions. It is also necessary to determine the bleeding and the coagulation time as well as the clot retraction. It is not within the scope of this paper to describe the standard methods used.

CLASSIFICATION OF PURPURA

At first purpuric diseases were classified according to clinical manifestations. Later the data furnished by hematologic investigations

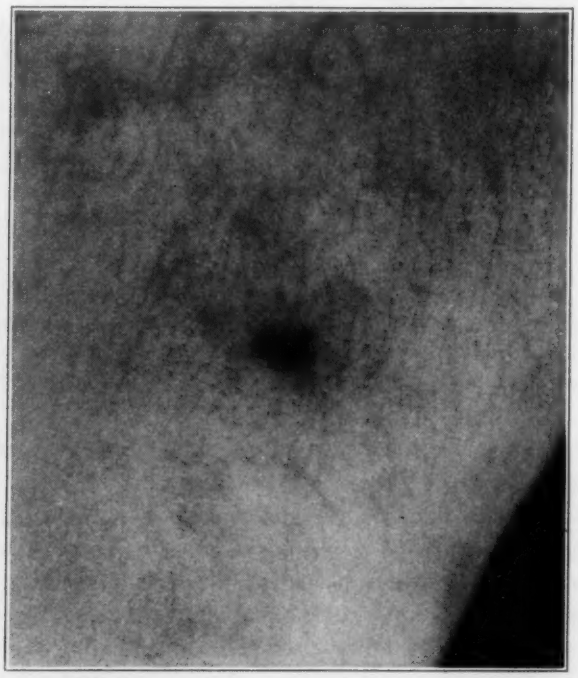

Fig. 1.—Positive reaction to venom on the leg at the end of one hour in a patient with angioma serpiginosum. Note the background of netlike erythema.

established a more accurate separation of this group.[8] More recently experimental and physiologic studies on capillaries have again altered

8. Hammer, F.: Hemorrhagica Krankheiten, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 6, pt. 2, p. 512. (A complete bibliography on purpuric diseases until 1928 can be found in this monograph.) Glanzmann, E.: Beiträge zur Kenntnis der Purpura in Kindesalter, Jahrb. f. Kinderh. **83**:271 and 379, 1916; Erwiderung auf vorstehende Bemerkungen von Bessau- "Zur Frage der anaphylaktoiden Purpura," ibid. **84**:302, 1916.

the conceptions of purpuric diseases. With the introduction of moccasin venom and its more specific action on vessel wall structures, the field of investigation of purpuric diseases has been widened. The classification used in this report was founded on clinical, hematologic and capillary studies, especially with the use of moccasin venom, both as a test and as a therapeutic agent. We have followed, in the main, the original classification proposed by Rosenthal,[9] with the modifications resulting from the use of venom (table).

HISTOLOGY OF PURPURA

Most authorities have said little on the subject of the comparative histology of purpura. Even Gans [10] maintained that this chapter is unsatisfactory histologically because of the monotony of the changes. The histologic alterations have been divided into the changes seen early and those seen late. In early lesions the red blood cells are still intact and the vessels may or may not show rupture. In older hemorrhages the red blood cells are not intact and the vessels may show degenerative changes such as hyalinization, necrosis, endarteritis and thrombus formation.

It must be realized that to obtain an adequate histologic picture of what happens in any one of the group of purpuric diseases not only must a fairly large series of cases of any one type of condition be studied but also various stages in the course of the disease should be observed. Some of the material is difficult to study because of its rarity. Although we had a great deal of autopsy material available, it was decided to use clinical material only to avoid basing conclusions on misleading postmortem changes. It was for this reason that an attempt was made to acquire an experimental approach to this problem. The histologic picture of the purpuric lesions thus produced plus the rather scant biopsy material which we had available are presented in this report. It is intended that with the present report as a basis a more comprehensive histologic study of purpuric lesions will be attempted.

Experimental purpura was produced in normal persons and in patients with various diseases in an attempt to exemplify the two primary mechanisms of the production of purpura, i. e., diapedesis and rhexis. As an example of purpura due to diapedesis, petechiae were produced by means of suction. Purpura due to rhexis was exemplified by the ecchymosis following the intradermal injection of measured amounts of titrated moccasin venom. We believe that stasis leads to

9. Rosenthal, N.: The Blood Picture in Purpura, J. Lab. & Clin. Med. **13**: 303, 1928.

10. Gans, Oscar: Histologie die Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1, p. 380.

Relationship of Hematologic and Dermatologic Purpura to Intradermal Moccasin Venom

I. Purpura Associated with Thrombocytopenia

A. Idiopathic Thrombocytopenic Purpura Haemorrhagica

	Associated Diagnostic Criteria	Results of Venom Test
1. Cases of acute disease with recovery	Purpura and ecchymoses, bleeding gums; no anemia, prolonged bleeding time, positive tourniquet test, no clot retraction; platelets usually less than 80,000	Positive with reversal on improvement
2. Cases of acute disease with fatal termination	Bleeding from mucous membranes and skin; 10,000 or less platelets; death from loss of blood	Always strongly positive
3. Cases of chronic disease with symptomatic improvement from venom therapy	Positive tourniquet and flicker test, no clot retraction; these signs reversing as result of venom therapy, but thrombopenia persisting	Positive initially with reversal; finally negative
4. Cases of chronic disease without symptomatic improvement from venom therapy	No change in laboratory and clinical signs as result of venom therapy	Persistently positive
5. Cases of recurrent diseases	Laboratory and clinical signs varying in relation to remission or relapse; venom therapy apparently aiding in producing remission	Positive during exacerbations; negative during remissions
6. Cases in which splenectomy was performed	Operation effecting cures in some cases and having no influence in others	
(a) Improvement from venom therapy and splenectomy	.....	Positive with reversal to negative on venom therapy or immediately after splenectomy
(b) Improvement from splenectomy and not from venom therapy	.....	Persistently positive; negative after operation
(c) No improvement from splenectomy or from venom therapy	.....	Persistently positive before and after operation

B. Diseases with Secondary Thrombocytopenic Purpura Haemorrhagica

1. Leukemia	Leukemic process with many or few abnormal blood cells (myeloid, lymphoid or monocytoid) in peripheral blood stream involving bone marrow and through infiltration crowding out the megakaryocytes and reducing the number of platelets; clinically, usually anemia, lymphadenopathy and splenomegaly; purpura usually occurring only when platelets number less than 40,000	Positive when number of platelets is diminished
2. Aplastic anemia	Number of red cells, white cells and platelets reduced; marrow hypoplastic; purpura occurring late in the disease as a rule	No tests made
3. Pernicious anemia	Macrocytic anemia with an associated hyperplastic megaloblastic marrow; purpura occurring when the number of platelets is greatly diminished	Negative (?) (only two cases observed)
4. Splenomegalic cirrhosis	Splenomegaly and anemia with reduced number of platelets; purpura occurring late in the disease	Negative
5. So-called Banti syndrome	Anemia, leukopenia, hepatosplenomegaly, gastric hemorrhages and purpura occurring when the number of platelets is diminished	Negative
6. Gaucher's disease	Anemia with hepatosplenomegaly; Gaucher cells infiltrating bone marrow causing thrombopenia with resulting purpura; pingueculae and pigmentation of the skin of the legs also characteristic	Negative
7. Subacute bacterial endocarditis	Anemia, septic fever, organic heart disease, thrombocytopenia with bacterial emboli causing purpura or capillary thrombotic inflammations	Negative

Relationship of Hematologic and Dermatologic Purpura to Intradermal Moccasin Venom—Continued

	Associated Diagnostic Criteria	Results of Venom Test
I. Purpura Associated with Thrombocytopenia—Continued		
C. Purpura due to Drugs		
1. Sedormid (allylisopropylacetylcarbamide) 2. Arsenic (neoarsphenamine) 3. Gold 4. Chrysarobin	Diagnosis made by history of the use of the drug and by reelicitation of the purpura by the drug; distinct thrombopenia occurring with the purpura	Positive (sedormid); reversal on removal of the causative factor; first indication of improvement
II. Nonthrombocytopenic Purpura		
A. Hematologic and Clinical Condition		
1. Thrombo-asthenic purpura	Generalized purpuric and ecchymotic manifestations but normal number of platelets; clot retraction poor indicating platelets of poor quality	Positive
2. Schönlein's purpura peliosis rheumatica	Hemorrhages into joints, characteristic; platelets usually normal in numbers; tourniquet test usually positive during relapse	Phasically positive
3. Henoch's purpura	Hemorrhages into intraabdominal organs; platelets usually normal in number	Phasically positive
4. Nitrogen retention	Purpura occurring infrequently during nephritis	Negative (?) (test used in only one case)
5. Endocrinous purpura; menopausic purpura	This purpura rather infrequently seen, but associated with endocrinous disturbances or history of menopause	Reversal under treatment
6. Cholemia and jaundice	Purpura in jaundice probably due to capillary irritation because of increased bilirubin	Usually positive
7. Hemophilia	Familial history and episodes of hemarthroses and generalized hemorrhages; increased coagulation time	Negative
8. Bacterial infections (streptococcic, staphylococcic or meningococcic, pneumonia)	Positive culture; embolic phenomena (embolism and thrombosis of capillary) and leukocytosis and fever, characteristic	Negative
9. Virus diseases (smallpox, measles	History and cutaneous lesions and course of disease, characteristic	Positive at site of greatest purpura; German measles only disease studied
10. Syphilis	Positive Wassermann reaction and vascular involvement	Negative
B. Nutritional Disturbances		
1. Scurvy	History of dietary deficiency, especially deficiency of fruits; diffuse purpura, subperiosteal hemorrhages, tender bones, bleeding gums with immediate improvement when fruit juices are given, characteristic	No tests made
C. Associated Dermatologic Conditions		
1. Majocchi's disease	Short duration; purpura always present; atrophy of hair follicles; histologically, obliterating endarteritis and hemorrhage	No tests made
2. Angioma serpiginosum	Many years' duration; no atrophy of hair; no purpura; histologically, no hemorrhage or proliferation of endothelial cells of larger vessels and capillaries	Positive
3. Schamberg's disease	No subjective symptoms; purpura present; long duration and progressive atrophy sometimes present; histologically, proliferative endarteritis; pigmentation consisting of old hemorrhage and giving reaction for iron	No tests made
4. Pigmented purpuric lichenoid dermatitis	Pigmented papules becoming purpuric or telangiectatic; course extremely chronic; distinguished from Schamberg's disease by papular lesions; histologically, endarteritis and intracellular and extracellular iron pigment granules	No tests made

Relationship of Hematologic and Dermatologic Purpura to Intradermal Moccasin Venom—Continued

II. Nonthrombocytopenic Purpura—Contined

C. Associated Dermatologic Conditions—Continued

	Associated Diagnostic Criteria	Results of Venom Test
5. Kaposi's disease	Sarcoma of the blood vessels, especially of small vessels of the skin; number of platelets sometimes diminished	Positive (one case)
6. Osler's disease	Multiple telangiectases, chronic nasal hemorrhage	Negative
7. Angiomatous nevi	.....	Negative
8. Orthostatic purpura	Usually congenital weakness of capillaries; usually capillary stress occurring while standing cannot be withstood in capillaries of lower extremities	Positive on leg; negative on arm
9. Dermatitis haemastatica	Purpura due to blood hemastasis usually due to weakness of vessel walls	Positive during active seepage

degenerative changes in the vessel walls and is thus a contributing factor in the formation of purpura, but it is not a separate mechanism.

METHODS OF PRODUCTION OF EXPERIMENTAL PURPURA

Purpura Diapedesis.—A suction cup attached to a strong rubber bulb, a part of a snake bite treatment outfit, was used. The skin was cleansed with alcohol and thoroughly dried, and suction was applied to the area, the maximum negative pressure (minus 40 cm. of mercury) being used. This was allowed to remain on the skin for from five to fifteen minutes.

Purpura by Rhexis.—Titrated moccasin venom used for the cutaneous test was injected intradermally in amounts of from 1 to 2 units of hemorrhagin (0.1 to 0.2 cc. of the 1 : 3,000 solution).

MATERIAL STUDIED

A. Normal Skin.—Studies were made on Mrs. R., aged 39, who had an apparently normal skin and was being treated for an inoperable carcinoma of the cervix.

Purpura by Diapedesis.—A suction cup was applied to the flexor surface of the right forearm 5 cm. below the elbow. It was allowed to remain in contact under maximum negative pressure of the apparatus for fifteen minutes. At the end of that time the area exposed to suction was diffusely red, and at the periphery there were a moderate number of petechiae. A specimen for biopsy was taken from the periphery forty-five minutes later.

Histologic examination showed little free hemorrhage in the tissue. In the papillary and subpapillary layers there were a number of dilated capillaries moderately engorged with blood. The vessel walls in nearly all instances appeared to be intact. The endothelial cells lining these vessels appeared to be flat. The hemorrhage, when it was present, surrounded apparently intact vessels in most instances. No inflammatory exudate was seen. In a number of instances there was a suggestion of diapedesis of the red blood cells in their relation to the endothelial cells (fig. 2*A*). In such instances the spaces between the endothelial cells seemed widened. In the vicinity of the hemorrhage the elastic tissue seemed fragmented.

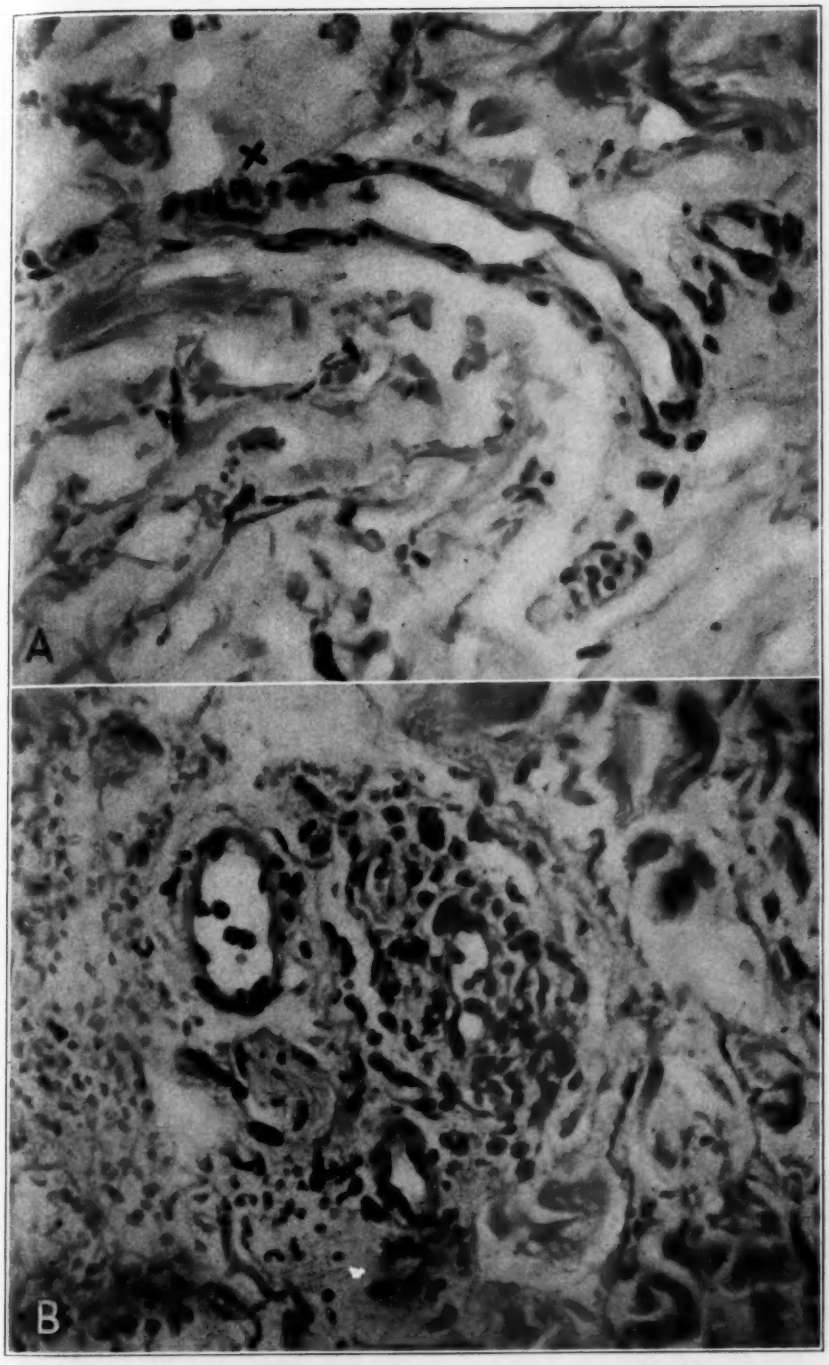

Fig. 2 (case A).—Photomicrographs of sections stained with hematoxylin and eosin (× 400). *A*, petechiae produced by suction in normal skin. Dilated capillary with suggestion of diapedesis of red blood cells (*x*). No inflammatory exudate is present. Spaces between endothelial cells are widened. *B*, reaction to injection of 2 units of hemorrhagin in normal skin. Dilatation of vessels, some perivascular infiltration and inflammatory changes in the vessel wall are noticable.

Purpura by Rhexis.—Two units of venom was injected intradermally in the flexor surface of the left forearm at the level at which the suction had been applied. At the end of one hour the reaction was negative but the site of injection showed a moderate amount of swelling. Material for a biopsy was removed from the center of the site of injection one hour after the injection.

Histologic examination showed that in the basal layer and especially around the hair follicles there was intracellular edema which in some instances went on to an aborted vesicle formation. The tissue of the subpapillary and papillary layers took the eosin stain poorly and showed edema. At that level there were a number of dilated vessels and lymph spaces. The vessels were filled with red blood cells. In the middle and lower layers of the cutis the "minute vessels" were mainly affected, but even the arterioles were involved. There was a moderate amount of hemorrhage, situated mainly in the subpapillary and middle layers of the cutis. The changes in the vessel were moderate. In a few instances there was rhexis of the vessel walls with a break in the vascular continuity. In others there was just vascular dilatation, and some of the endothelial cells appeared to bulge into the lumen. The hemorrhage seemed to be in the vicinity of the affected vessels. There was a moderate amount of inflammatory exudate consisting of leukocytes (fig. 2*B*). The elastic tissue was fragmented in the area of hemorrhage.

B. Experimental Purpura in Chronic Purpura Haemorrhagica.—L. E., a married woman aged 47, had typical purpura haemorrhagica. She had received venom therapy since March 8, 1935. The clinical manifestations had been controlled, but the blood picture was not improved by the therapy. The venom test had become negative as a result of treatment.

Purpura by Diapedesis.—Suction was applied to the flexor surface of the right forearm under maximum negative pressure of the apparatus for five minutes. The area exposed was diffusely red and showed many more petechiae than the normal skin. Again the petechiae were most numerous at the periphery. A biopsy was performed on March 27, 1936, material from the periphery being obtained thirty minutes after the removal of the suction cup.

Histologic examination showed that the vessels of the subpapillary and the middle layer of the cutis were mainly affected. A greater degree of hemorrhage was present than had been observed in the normal skin after suction had been applied, and there were many dilated and engorged blood vessels. The hemorrhage was seen to be due in many instances to complete rupture of the smaller vessels without any apparent change of the endothelial cells. There was no inflammatory exudate, but there was marked edema in the tissues surrounding the vessels. Fragmentation of the elastic tissue was seen in the area of hemorrhage.

Purpura by Rhexis.—Two units of moccasin venom was injected into the flexor surface of the left forearm. Forty-five minutes later the reaction was practically negative, and material for a biopsy was taken from the center of the swelling produced by the injection.

Histologic examination showed changes in the vessel through all the layers of the cutis. While the changes were greater in degree than those seen in the normal skin, they were relatively moderate in amount. Not only the capillaries but the venules and arterioles showed the effects of the venom. The changes varied from dilatation and engorgement of the vessels to frank destruction of vessel walls. Apparently where the venom was present in greatest concentration the tissues were digested and in that area the greatest degree of free hemorrhage and the most marked changes in the vessel walls were observed. In the

vicinity of some of the affected vessels there was a moderate amount of leukocytosis. Instead of the rupture seen after suction there was a marked effect on the elements of the vessel wall so that component parts could not be recognized. It was difficult to note a transition from endothelial swelling to complete degeneration. The elastic tissue was markedly fragmented in areas of hemorrhage, and there was striking edema of the surrounding tissues.

C. Experimental Purpura in Chronic Purpura Haemorrhagica Refractory to Venom Therapy.—S. C., a woman aged 38, presented typical chronic thrombocytopenic purpura. She had received treatment with venom since June 19, 1934. There had been no response to the venom therapy, and the patient had continued to show purpuric eruptions, nasal hemorrhages and prolonged menstrual periods. The venom test was persistently positive. The patient had refused to undergo a splenectomy.

Purpura by Rhexis.—One unit of moccasin venom was injected intradermally into the flexor surface of the right forearm. There was a markedly positive reaction at the end of a half-hour. Material for biopsy was taken from the center of the lesion in January 1936.

Histologic examination showed a great deal of free hemorrhage throughout the section. The greatest amount was seen in the middle portion of the cutis. There was a much more intense pathologic change than in any of the sections previously described. Many of the capillaries and venules were markedly dilated. A striking feature was the leukocytic exudate. Many of the "minute vessels" as well as the arterioles in the deeper layers of the cutis showed a total destruction of their walls. The affected vessels showed an indiscriminate arrangement of red blood cells, leukocytes and fibroblasts apparently lying free in the tissues (fig. 3). At the periphery of the most intense reaction the capillaries and venules showed swelling of the endothelial cells. The arterioles showed leukocytic infiltration of the walls. Among the leukocytes were many eosinophils. In the area of most intense hemorrhage there was a marked toxic effect on the cutis fibers with a digested appearance more intense than that described previously. The elastic tissue seemed fragmented and markedly diminished in the papillary and subpapillary bodies. This change was most marked in areas of hemorrhage.

D. Spontaneous Petechiae.—Material for biopsy was taken from a shower of petechiae on the right thigh of S. C. (*C*). The lesions had been present several days.

Histologic examination showed that the epidermis was practically normal. In the papillary and subpapillary layers of the cutis there were a number of dilated capillaries, some of which were engorged with blood. There was a small amount of free hemorrhage immediately surrounding some of the dilated vessels. The endothelial cells were unchanged. However, the elastic tissue seemed fragmented and diminished. There was no inflammatory exudate. The picture resembled that of purpura caused by suction.

E. Persistent Purpuric Lesions Above the Ankle in Chronic Thrombocytopenic Purpura Refractory to Venom Therapy.—Mrs. LaC., aged 43, had typical clinical and histologic manifestations of chronic thrombocytopenic purpura. The disease was of many years' duration. It had not responded to venom therapy after several years of treatment. The venom test was persistently positive. The spleen had been removed, but no clinical or hematologic improvement had resulted. Lesions of purpura occurred frequently. The purpuric areas around the ankles had existed for many months (fig. 4). Material for biopsy was obtained from the center of one of the old purpuric lesions on the lower third of the leg.

Histologic examination showed that the epidermis was atrophic and the papillary bodies were flattened. There were few intact red blood cells, but there was a great deal of blood pigment lying free in the tissues throughout the middle layers of the cutis. The capillaries were dilated and seemed to be in stasis. In the lower portion of the cutis there was a large tortuous arteriole with thickened walls. The lumen was narrow. This particular vessel was much larger than is usually seen in that part of the skin. There was a moderate amount of inflammatory exudate in the surrounding tissues. The elastic tissue was fragmented and diminished.

F. SCHÖNLEIN-HENOCH'S PURPURA.—J. S., a man aged 51, had been ill for five weeks. The illness began with a diffuse cutaneous eruption, malaise, polyarthritis

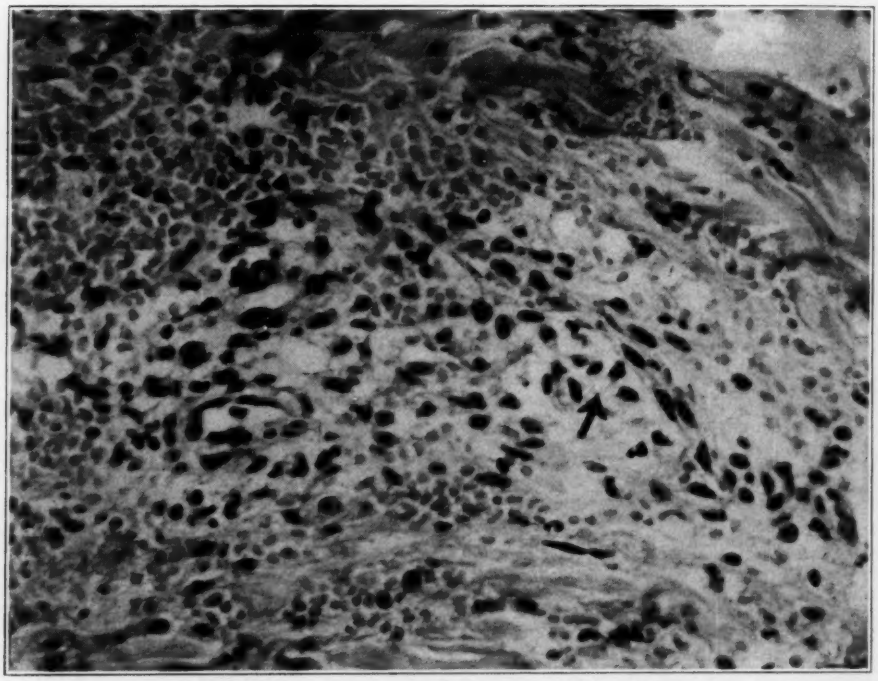

Fig. 3 (case C).—Photomicrograph of a section from the site of a positive reaction to venom in a case of chronic thrombocytopenic purpura not responding to venom therapy (hematoxylin and eosin; × 400). A great deal of free hemorrhage, more intense reaction, total destruction of vessel, so that the component parts are not recognized, and marked leukocytosis are present.

and a sore throat. When the patient was seen on April 18, 1936, he presented what appeared to be erythema multiforme. The venom test was negative. By May 2 the eruption had become distinctly purpuric; the temperature rose to 101 F., and the venom test had become strongly positive in all regions of the body. The blood picture showed no evidence of a hemorrhagic diathesis, but the presence of toxic granules indicated some infectious process. By May 15 the patient had begun to improve, and the venom test had become negative. Material for a biopsy was obtained from the center of a large purpuric lesion on the left arm on May 5.

Histologic examination showed minimal epidermal changes. A marked inflammatory exudate was seen throughout the section. The hemorrhage was masked by the leukocytosis, but on analysis it could be seen that most of the inflammatory exudate was really perivascular (figs. 5 *A* and *B*). The exudate consisted mainly of leukocytes, but there were a number of mononuclear cells. The endothelial cells in a number of areas were apparently swollen and protruded

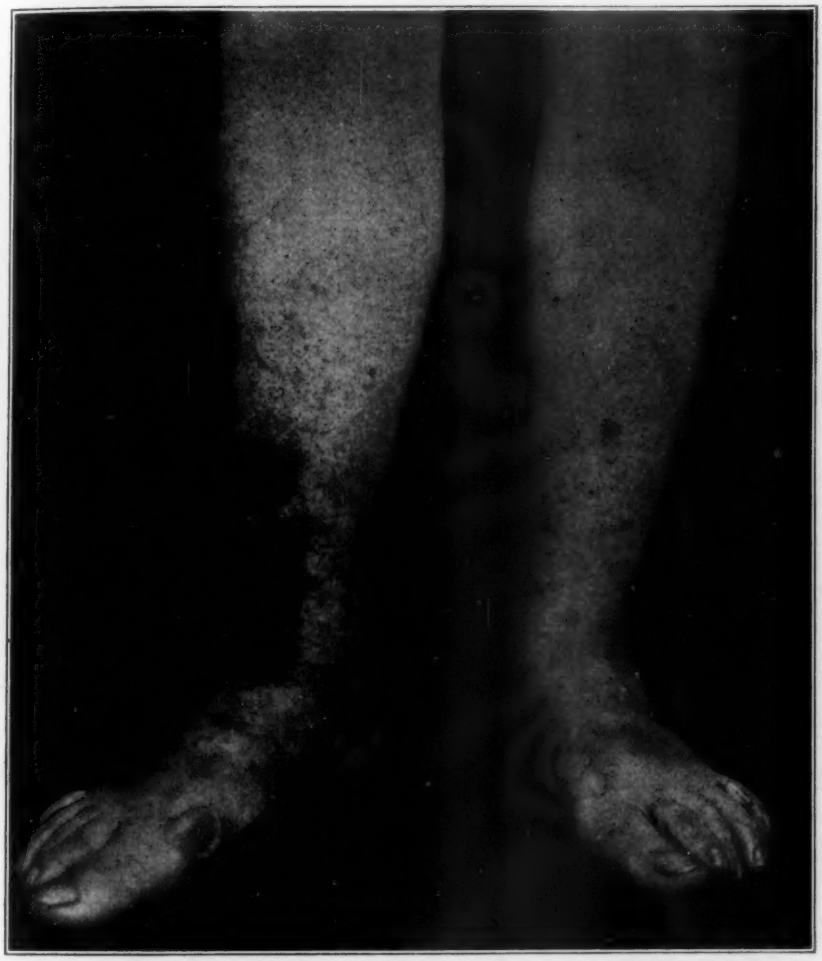

Fig. 4 (case E).—Purpuric eruption of long duration in a patient with chronic thrombocytopenic purpura not responding to venom therapy or to splenectomy.

into the lumen. Rhexis of the vessels due to destruction of the wall could also be seen. The arterioles as well as the capillaries and venules were affected. Where the exudate was around arterioles there was, of course, an infiltration of the walls with leukocytes. Although there was a marked inflammatory reaction, the elastic tissue was well maintained. In the actual area of exudate it was

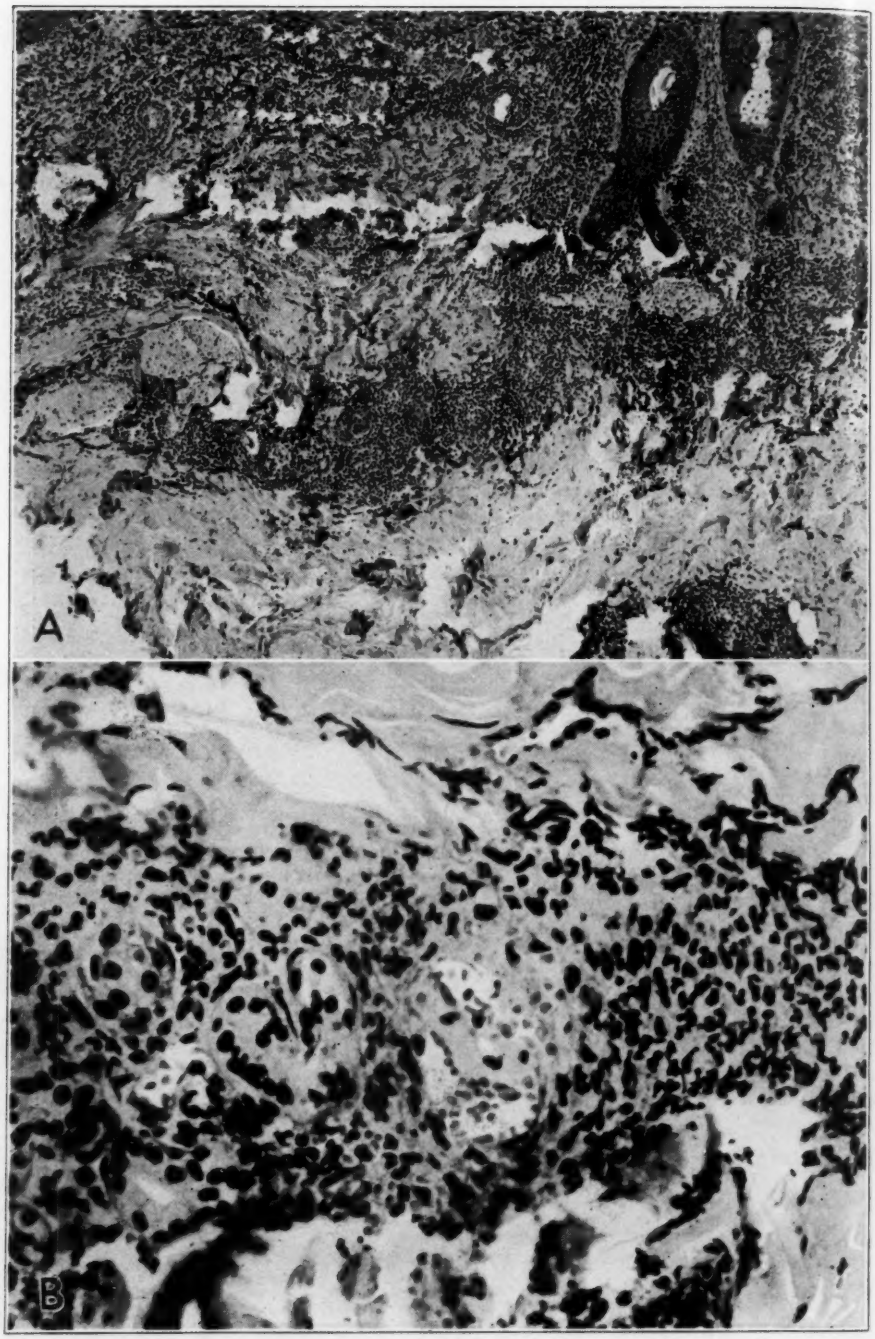

Fig. 5 (case F).—*A*, photomicrograph of a section of tissue from a purpuric lesion on the arm of a patient with an active stage of Schönlein-Henoch's purpura (× 70). There is marked inflammatory reaction throughout the section, consisting mainly of perivascular changes plus hemorrhage. *B*, higher magnification of the section shown in figure 5 *A* (hematoxylin and eosin; × 400). Rhexis of the vessel wall, swelling of endothelial cells, hemorrhage and marked perivascular infiltration with leukocytosis are present. The changes resemble the reaction shown in figure 3.

fragmented, but it was much more abundant than in the section to be described immediately after this. The reaction resembled that seen after the introduction of vonom in case C (fig. 3).

G. SCHÖNLEIN-HENOCH'S PURPURA.—P. S., a man aged 32, stated that he had recurrent purpuric lesions limited to the legs. Four months before pains in the knees and a sore throat had developed. The blood picture was normal except for an eosinophilia, the percentage of eosinophils being 15. On both legs, especially toward the ankles, there were many petechiae and small ecchymoses. The venom test on May 2 was positive only in the vicinity of the eruption, not on the thigh or arms. By May 15, as a result of rest in bed, the lesions had practically disappeared and the venom test had become negative. There was no fever at any

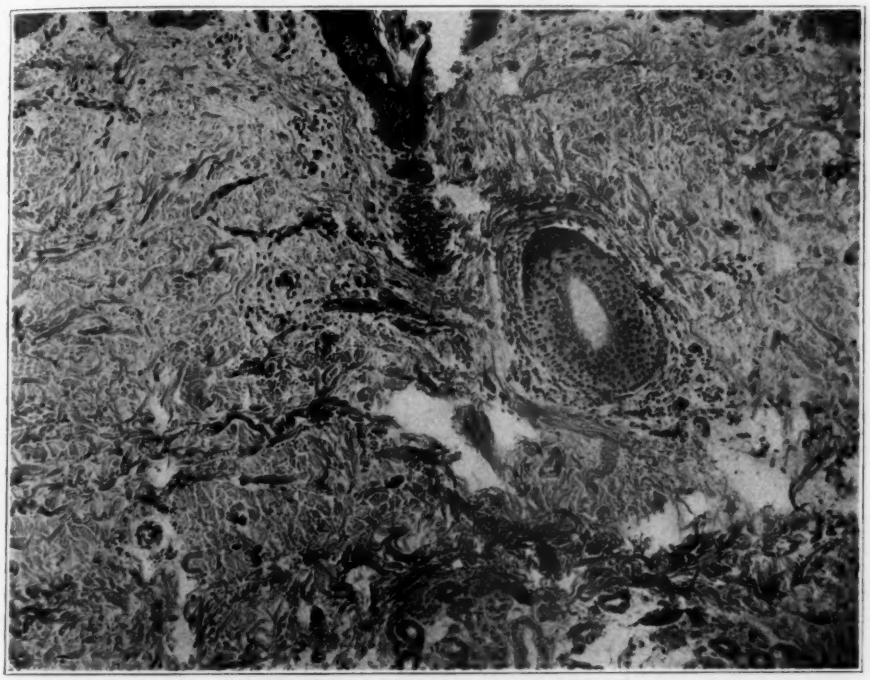

Fig. 6 (case G).—Photomicrograph of section from a lesion of purpura affecting the leg only of a patient with Schönlein-Henoch's purpura (× 80). The venom test was positive only on the leg. Minimal inflammatory reaction and dilatation of capillaries in the upper portion of the cutis are present.

time during the patient's stay at the hospital, and no symptoms in the joints were noted. A number of internists were inclined to classify the disease as hemostatic purpura. Material for biopsy was obtained on May 5 from one of the lesions above the right ankle.

Histologic examination showed that the epidermis was practically normal except for some hyperkeratosis. The hemorrhage was observed just below the papillary layer in a linear arrangement. The capillaries in the papillary and subpapillary bodies were dilated, and a number seemed to be ruptured. Endothelial cells in the ruptured ones seemed to be unchanged, and no inflammatory or degenerative change was seen. The arterioles in the deeper layers were not

affected. Changes were suggestive of those seen after the application of suction (fig. 6). The elastic tissue throughout the section was diminished and fragmented.

H. SCHÖNLEIN-HENOCH'S PURPURA.—Mrs. H., aged 50, presented a recurrent purpuric eruption on the lower extremities which would appear and regress. This had been preceded by a sore throat and symptoms in the joints a few months previously. At the time the biopsy was made there was a discrete but markedly widespread purpuric eruption extending from the ankles to a little above the thighs (fig. 7). The purpuric lesions were deep blue, about 0.33 to 0.5 cm. in diameter and, in a number of instances, distinctly papular. A venom

Fig. 7 (case H).—Purpuric eruption on the legs of a patient who had Schönlein-Henoch's purpura several months previously. The venom test was negative.

test was negative both on the leg and on the arms. This was interpreted as indicating the inactivity of the process at the time the test was made. Material for a biopsy was taken from a lesion on the middle of the leg.

Histologic examination showed many dilated vessels filled with blood throughout all the layers of the cutis. The red blood cells were indistinct and seemed to lie in a sort of coagulum or fibrin within the vessels. The blood vessels were markedly dilated as if in stasis. In such vessels the walls seemed indistinct, while the endothelial cells took a fairly good stain, but the spaces between the endothelial cells seemed widened (fig. 8*A*). The larger, thin-walled vessels

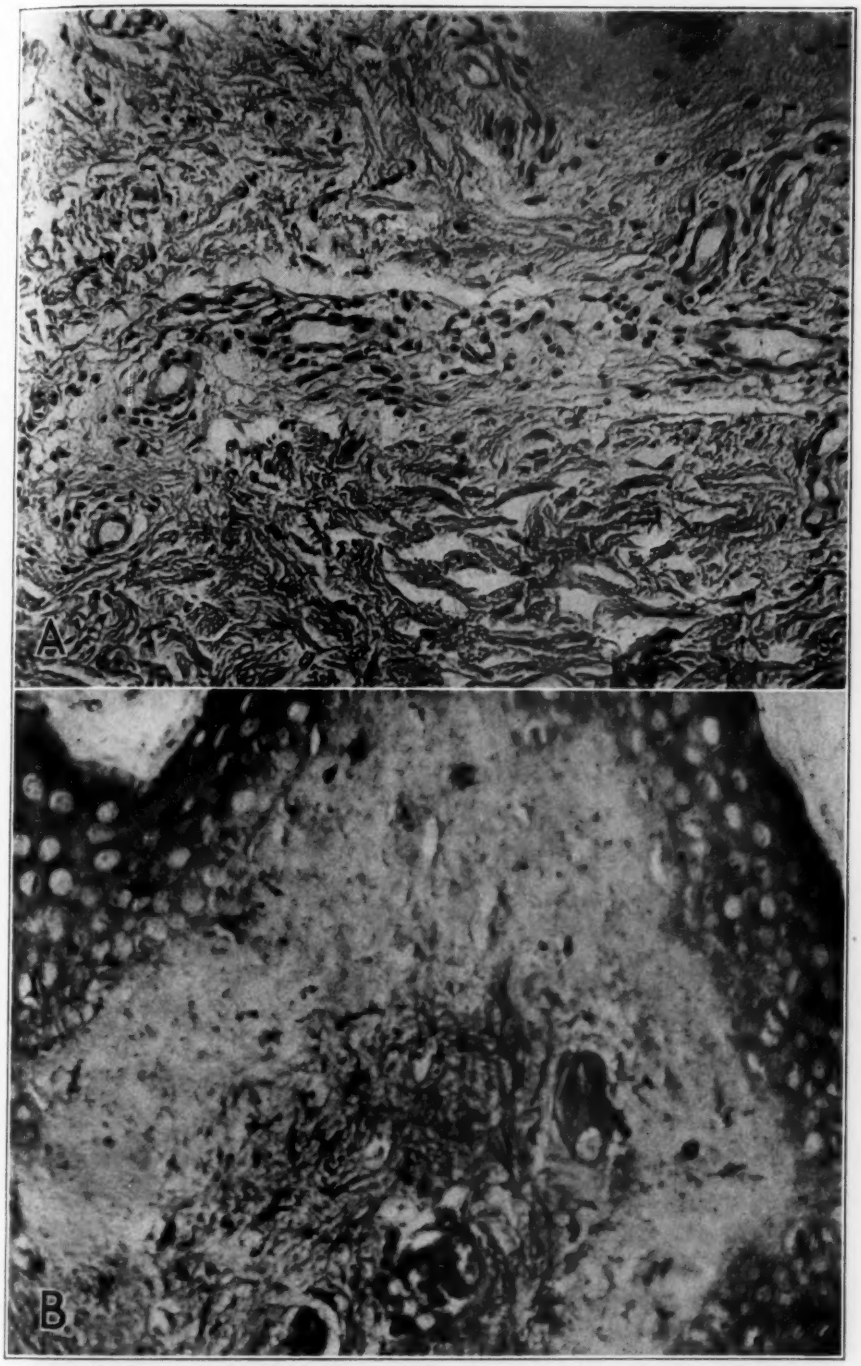

Fig. 8 (case H).—*A*, photomicrograph of section of purpuric lesion on the leg (hematoxylin and eosin; × 220). Dilated small vessels with widened space between endothelial cells are noticeable. The endothelial cells seem indistinct in some instances. Capillaries seem to be in stasis. No inflammatory exudate is seen. *B*, photomicrograph showing fragmentation and diminution of the elastic tissue in the cutis (Weigert's elastic tissue stain, × 220).

(venules?) seemed to show changes in the endothelial cells. The arterioles were fairly well maintained, and only a few showed changes. The hemorrhage was seen in the lowest layer of the cutis, and the red blood cells were indicated by faint shadows. No actual rupture of a vessel wall was seen. There was a large number of dilated capillaries in the upper layers of the cutis, the walls of many of which seemed rather indistinct. The boundaries of the endothelial cells were not sharp. The tissue of the subpapillary and papillary bodies seemed to take the stain poorly and appeared rather granular and homogeneous. The elastic tissue was not only fragmented but diminished throughout the section (fig. 8*B*).

I. Schönlein-Henoch's Purpura.—A. v. S., a woman aged 57, had an eruption of three weeks' duration accompanied by aches and pains. At the time biopsy material was obtained from the arm she presented on the extremities, especially on the flexor surfaces, red lesions from the size of a pinpoint to that of a pinhead which did not disappear on pressure. The hematologic examination gave negative results. The venom test was negative.

Histologic examination showed that the epidermal changes were not important. The papillary and subpapillary layers showed dilated vessels, most of which were engorged with blood. The endothelial cells seemed unchanged, although the spaces between these cells seemed widened in some instances. No inflammatory exudate was seen. The elastic tissue was diminished in the papillary and subpapillary bodies. It was not diminished to any appreciable extent in other parts of the section except that it was fragmented in the upper portion of the cutis.

COMMENT AND SUMMARY OF HISTOLOGIC CHANGES

The difference between hemorrhage due to mechanical factors such as suction and that due to the effect of a toxin could be clearly seen by the presence of an inflammatory reaction in the latter. Leukocytosis occurred from thirty to forty-five minutes after the introduction of the venom. In cases of hemorrhage by diapedesis and its further extension to complete rupture of the vessels the endothelial cells were unchanged. When toxic action caused hemorrhage there was a dissolution of the vascular continuity with accompanying changes in the endothelial cells and in the vessel wall itself. It was evident from the histologic changes that the elastic tissue of the cutis apparently played a definite rôle in the formation of purpura. Trauma such as negative pressure caused a rupture of the elastic tissue while the toxins also had a direct effect on it.

Apparently this elastic tissue acts as a supporting structure for the capillary walls and plays a definite rôle as a shock absorber in the prevention of undue stress and strain on these vessels. This could be seen by comparing the changes in the elastic tissue in the purpura produced by suction in normal and in diseased skins. The greatest degree of rupture was of course produced in patients with fragile vessel walls, and it was in those patients that the elastic tissue was diminished. The rôle of the elastic tissue was especially noticeable in the purpuric material from the lower extremities of patients with Schönlein-Henoch's disease. In the acute stages of this syndrome purpuric manifestations

are seen all over the body. In P. S., Mrs. H. and A. v. S. (cases G, H and I) the process was in the stage of regression or was a sequela of the disease itself. The purpura was usually restricted to the extremities, and the venom test in Mrs. H. and in A. v. S. (cases I and H) was negative. It was striking to note that the elastic tissue was diminished and fragmented, especially in the portions of the cutis where the hemorrhage was seen.

In discussing the classification of purpuric eruptions from the standpoint of histologic changes and of the reactions to venom, the four cases of Schönlein-Henoch's purpura described (cases F, G, H and I) serve as excellent examples. In the case of J. S. (case F) the venom test was positive all over the body. The histologic picture was like that of the experimental purpura produced by the venom and represented an acute toxic inflammatory process. In P. S. (case G) the venom test was positive only on the ankle and the histologic picture was like that of experimental purpura produced by suction in diseased (purpuric) skin. Mrs. H. and A. S. (cases H and I) had negative reactions to venom, and the histologic picture in their skins was practically the same as in that of P. S. (case G). On the basis of the histologic changes and the reaction to venom it can be said with certainty that different stages of the syndrome were present.

In J. S. (case F) the active toxic process was still manifest. In P. S. (case G) hemostatic factors were definitely playing a rôle, although there was still some capillary fragility as shown by the venom test. In Mrs. H. and in A. S. (cases H and I) an end-process was evident. Hypostasis and not capillary fragility plus the lack of an adequate elastic tissue mantle in the cutis around the static capillaries deprived them of an adequate support so that an increased intracapillary pressure produced manifestations of purpura. These purpuric lesions apparently occurred mainly by the mechanism of diapedesis, and on a further yielding of the vessels there was a mechanical rupture.

The spontaneous petechiae in patients with thrombocytopenic purpura were also apparently produced by diapedesis. In the early stages of Schönlein-Henoch's purpura there was a direct toxic effect on the vessel walls and the surrounding structures, including the elastic tissue. This was comparable to the purpura produced by the venom. As a result of the loss of elastic tissue and of a weakening of the vessel walls purpuric manifestations occurred in the lower extremities in the later stages of this disease. Apparently the elastic tissue in the cutis plays an important rôle in the mechanism of purpura.

VENOM THERAPY

Dosage for Adolescents and Adults.—The initial dose for patients over 10 years of age was 0.4 cc. of the 1:3,000 solution given sub-

cutaneously. The amount was rapidly increased in subsequent injections to 1 or 2 cc. The injections were given in the arm or in the thigh. In the majority of cases the injections were given twice weekly. If there were marked symptoms of bleeding daily injections of 1 or 2 cc. could be given. Treatment was given twice a week for two or three months, depending on the type of condition treated.[11]

For the best therapeutic results it was important that therapeutically active venoms be used and that enough of the venom be given. It has been advised in the presence of marked symptoms of bleeding that maximum doses be given daily until the hemorrhage stops. Two cubic centimeters administered in doses of 1 cc. morning and evening have been given daily without any ill effect for long periods.

Dosage for Children.—The same principle of treatment was applied in the case of children under 10 years of age except that the minimum dose was 0.2 cc. and the maximum dose was 1 cc. Such amounts have been given to infants without ill effects.

Reaction to Injections of Venom.[12]—An ecchymosis may develop at the site of injection in the first twenty-four hours. A number of the patients exhibited a reaction of hypersensitivity to the snake venom in about ten to fourteen days after beginning the treatment. The reaction was practically always local, and it was characterized by a hot tender swelling at the site of injection. No general reaction occurred. Daily injections of 1 cc. for sixteen days have been given to patients with scarlet fever without any ill effect to the kidneys.[13]

Desensitization.—In nearly all the cases desensitization was accomplished, and no general reaction was encountered in the process of desensitization. To accomplish desensitization two methods were used. The first and more simple procedure was attempted in the presence of marked symptoms of bleeding, and the second was used when the first failed or when the local reactions were too severe. With the first method the dose after the reaction of hypersensitivity was decreased to 0.05 cc. of the 1:3,000 solution. This usually caused a swelling, but unless it was large it was disregarded, and subsequent doses were increased cautiously until the required dosage was reached. Occasionally the reactions were too severe or desensitization could not be accomplished; the second method was then indicated. The following series of doses given

11. Peck, S., and Rosenthal, N.: Effect of Moccasin Snake Venom (Ancistrodon Piscivorus) in Hemorrhagic Conditions, J. A. M. A. **104**:1066 (March 30) 1935.

12. Peck, Samuel M.: Sensitization and Desensitization in Man with Snake Venom (Ancistrodon Piscivorus), Arch. Dermat. & Syph. **27**:312 (Feb.) 1933.

13. Lyttle, J. D.; Schneierson, S., and Peck, S. M.: The Effect of Moccasin Venom on Urinary Changes Following Scarlet Fever, Am. J. Dis. Child. **52**: 796 (Oct.) 1936.

twice a week was found satisfactory: 0.1 cc. of the 1 : 10,000 solution; 0.4 cc. of the 1 : 10,000 solution; 0.2 cc. of the 1 : 6,000 solution; 0.4 cc. of the 1 : 6,000 solution; 0.1 cc. of the 1 : 3,000 solution, and 0.4 cc. of the 1 : 3,000 solution.

CLINICAL EXPERIENCES

During the last five years the efficacy of moccasin venom in the treatment of hemorrhagic symptoms has been adequately proved.[14] Purpuric manifestations with few exceptions could be directly attributed to systemic or local disturbances of the capillaries with or without changes in the platelets. A positive reaction to venom usually indicated the need for venom therapy. It was of course understood that in cases of leukemia and of Gaucher's disease the purpuric manifestations were of secondary importance, and venom therapy was not suggested as a method of treatment.

There were a number of hemorrhagic states, such as hereditary familial telangiectasis and chronic nasal bleeding, as well as metromenorrhagia, which usually were not associated with a positive reaction to venom but yielded to venom therapy. This could be partly explained on the basis that the local areas where bleeding occurred were inaccessible to the test.

The venom test was used as a guide for the venom therapy. When a response to this form of treatment was noted there was a reversal from a positive to a negative reaction. In the same way a continued positive reaction after a period of sufficient treatment pointed to a failure of the venom therapy. The venom test even without the use of the venom therapy was of prognostic significance since repeated tests indicated the tendency of the purpura at the time the test was made. This was well illustrated in the treatment of thrombocytopenic purpura haemorrhagica.

It has been shown that in cases of acute purpuric disease a reversal from a positive to a negative reaction to venom accurately foretold clinical improvement before the hematologic status had changed appreciably. In patients with chronic involvement treated with venom the reversal of the reaction corresponded to clinical improvement while the hematologic picture remained unchanged. Furthermore, the patients with a chronic condition responding to venom therapy were apparently cured by splenectomy. Patients who did not respond to the venom therapy and showed a continued positive reaction to venom could be

14. (*a*) Peck, Samuel M.: Attempts at Treatment of Hemorrhagic Diathesis by Injection of Snake Venom, Proc. Soc. Exper. Biol. & Med. **29**:579, 1932. (*b*) Peck, Samuel M., and Goldberger, M. A.: The Treatment of Uterine Bleeding with Snake Venom (Ancistrodon Piscivorus), Am. J. Obst. & Gynec. **25**:887, 1933. (*c*) Peck, Rosenthal and Erf.[6b] (*d*) Peck and Rosenthal.[11]

cured or clinically improved by a splenectomy in some instances. In such patients the reaction to venom became negative within eight hours after the operation. A persistently positive reaction after splenectomy accurately prognosticated the future course of the disease, foretelling the failure of the operative procedure to improve the condition.

The two following types of conditions are presented because they, and closely allied ones, are frequently seen by dermatologists and present difficult problems of therapy. In addition, the conditions cited will serve as illustrations for the potentialities of venom in dermatologic practice. We believe that the suggested method of attack on capillary disease both from the diagnostic and therapeutic angles will probably lead to a better approach to this problem.

Type I: Hereditary Familial Telangiectases.[15]—These conditions belong to the vascular nevus group and have been proved to be hereditary and familial. In all of our seven cases a family history could be elicited, and in one instance it could be traced through three generations. In one instance a father and daughter were treated. Clinically the condition is characterized by telangiectatic lesions of the skin and mucous membranes which on the mucosa often form small varices. The patients complained of frequent and severe nasal hemorrhages. Often the hemoglobin content of the blood was reduced to a dangerously low level. Two cases of typical hereditary familial telangiectasis are reported.

CASE 1.—M. B., a 60 year old Russian Jew, said that he had frequent episodes of epistaxes sometimes daily for a period of nearly ten years. He also had attacks of asthma. His daughter had the same condition and was under treatment in our clinic. The patient was first observed at the Mount Sinai Hospital on April 9, 1934.

Physical examination gave negative results except for the telangiectases of the mucous membranes of mouth, nose and pharynx and small angiomatous nevi of the skin.

Laboratory studies including Wassermann and venom tests gave negative results.

A small angiomatous area was removed from the right arm. The epidermis was essentially normal. The upper and middle portions of the cutis showed a number of enlarged, thin-walled vessels engorged with blood.

Clinical Course and Treatment.—Venom therapy was started on April 9, 1934, 1 cc. of a 1 : 3,000 solution of venom being given twice weekly. The patient showed an immediate improvement and had only occasional slight hemorrhages until July. In July he had a severe nasal hemorrhage. For this reason the dose of venom was increased to 2 cc. twice weekly. This controlled the bleeding, and the subsequent injections were decreased to 1 cc. twice a week. The treatment has been continued twice weekly until the time of writing. As much as 3 cc. of venom has been given at one time in divided doses when contributing factors such as

15. Goldman, J. L.: Moccasin Snake (Ancistrodon Piscivorus) Venom Therapy for Recurrent Epistaxes, Arch. Otolaryng. **24**:59 (July) 1936. Peck and Rosenthal.[11] Peck.[14a]

asthma and colds with the associated increase in coughing and sneezing resulted in increased bleeding. There was no doubt that the incidence and amount of bleeding have decreased as a result of the venom therapy. The amount of venom injected varied with the symptoms of bleeding. Discontinuation of the venom therapy resulted in a recurrence of the bleeding.

CASE 2.—K. D., a man aged 30, had had bleeding from the nose since he was 8 years of age. Gradually the bleeding had become more severe and more

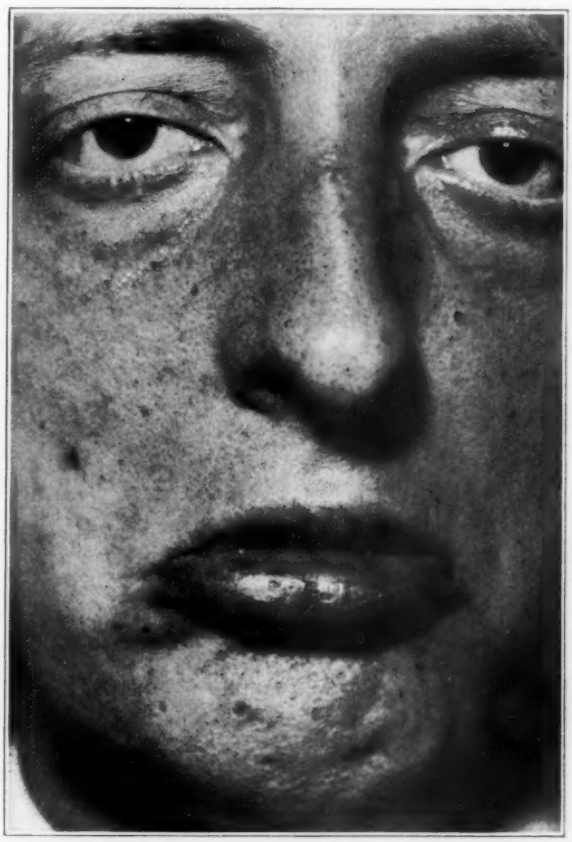

Fig. 9 (case 2).—Hereditary familial telangiectasia. Note the telangiectases on the mucosa of lip.

frequent. Many forms of treatment, such as local applications and electrocoagulation had all been without avail. When he first presented himself, on Oct. 2, 1935, he had had daily episodes of bleeding for the preceding six months.

Both his mother and his maternal grandmother had the same condition. His brother and sisters were free from it.

The patient was healthy, and physical examination gave negative results except for telangiectatic lesions of the nose, mouth, lips and cheeks. Under the tongue they appeared almost like small varices. Scattered telangiectases and small angiomas were present on the face and body (fig. 9). The Wassermann and the venom test were negative.

Histologic examination of material from a red angiomatous lesion on the left arm showed essentially the same picture as in case 1 (fig. 10).

Clinical Course and Treatment.—Venom therapy was begun on Oct. 2, 1935. One cubic centimeter of the 1 : 3,000 solution was given three times weekly. After a month of treatment there was some improvement. The dose was then increased to 2 cc. three times weekly. This was followed by a decided improvement, only a small nasal hemorrhage occurring occasionally. On occasions 3 cc. of venom (1.5 cc. in each arm) was given. While there was a definite improvement with venom therapy the patient still had a nasal hemorrhage occasionally.

Fig. 10 (case 2).—Photomicrograph of a section from a telangiectatic lesion on the arm (hematoxylin and eosin, × 220). Thin-walled vessels are present right below the epidermis.

On March 9 venom therapy was discontinued, and a marked tendency toward a recurrence of the former bleeding, though somewhat less severe, was noted. On March 27 large doses (200 mg. three times a week) of vitamin C (cevitamic acid) were given intravenously, but no appreciable amelioration of the bleeding was observed during the month in which this treatment was continued. Resumption of the injections of venom, 2 cc. being given three times a week, again resulted in improvement.

Summary of Type I: Patients with this condition bleed more frequently during the winter or during attacks of colds, sinus trouble and hay fever. Treatment with local remedies and even with radium was

of little value because of the inaccessibility of many of the lesions. Venom must be given in large doses and administered frequently to control the disturbance in many of the cases. As much as 6 cc. a week must be administered at the initiation of the treatment. After the hemorrhagic symptoms have been controlled to a certain extent a maintenance dose must be determined. This varied from 1 to 6 cc. a week. It should be emphasized that if therapy was discontinued there was a gradual recurrence of bleeding. In a number of the cases while the frequency and amount of the bleeding were diminished, they were not entirely controlled.

Type II: Vascular Disease of the Lower Extremities.—The following case is reported because it indicates that venom may be of use in a number of dermatologic conditions.

CASE 3.—*Diagnosis, angioma serpiginosum (?).*

A 28 year old nurse, born in the United States of Italian parentage, was first observed by one of us (S. M. P.) on Sept. 14, 1935, because of a generalized eruption on both legs of four years' duration. The family history was irrelevant. In October 1928 the patient was admitted to the Mount Sinai Hospital with the diagnosis of subacute appendicitis, cystitis and pleurisy. She stated that a tuberculous cervical gland had been removed when she was 16. She was readmitted on Nov. 2, 1928, to undergo an appendectomy, and at the operation a tuberculous lymph node was removed from the mesentery.

On March 2, 1934, the patient was again admitted because of pain in the left groin of three years' duration. Her menstrual flow was profuse and the periods were prolonged. Five weeks before her last admission maculopapular lesions had developed on both legs and an ulceration had appeared over the right internal malleolus. A few days after the patient was admitted the eruption consisted of small macular red lesions on both legs which in the course of the next few days became raised and nodular. Some of the nodules showed a central necrosis. Smears from these lesions contained no acid-fast organisms. The tuberculin test was strongly positive. Consent for a biopsy was refused. The diagnosis at that time was erythema induratum (Bazin's disease).

At our first observation (September 1935) the patient presented a widespread eruption on both legs extending from the ankles to the knees. The lesions consisted of minute bright red angiomatous puncta in groups. These formed irregular rings with clear central serpiginous zones. No definite bluish hemorrhagic areas were seen. The puncta were most marked from the middle of the calf to the ankles on both legs. There was a definite background of netlike erythema extending to a little above the knees. Over both internal malleoli there were superficial irregular ulcerations several centimeters in diameter. These were covered with a rather thick yellow crust (fig. 11). The thighs, especially right above the knees, showed fine vascular dilatations or varicosities of the type seen in women after pregnancy (fig. 12). No definite atrophy was seen. The patient stated that the eruption had started around the lower part of the leg and was gradually extending upward. She complained that pain in the legs and swelling of the ankles developed when she remained on her feet for a few hours.

The Wassermann reaction was negative; the reaction to tuberculin was strongly positive. The hematologic status was essentially normal.

Venom Test.—The venom test was performed on the right leg in the vicinity of the angiomatous puncta, above the knee and in the right arm. The reaction was intensely positive on the leg, delayed above the knee and negative on the arm.

Fig. 11 (case 3).—Lesion of angioma serpiginosum (Oct. 5, 1935). Angiomatous puncta in irregular rings with clear central zones and a background of netlike erythema ulcerations over the internal malleolus are noticeable.

Treatment.—Venom therapy was begun on Sept. 16, 1935, consisting of injections of 1 cc. of a 1:3,000 solution of moccasin venom twice weekly. Chlorhydroxyquinoline ointment was applied to the ulceration. The venom was injected in the arm or in the thigh. There was a rapid improvement in the clinical manifestations. By October 17 the venom test on the leg had become negative

and the ulcers had completely healed. In February 1936 the angiomatous puncta had disappeared and there was a marked fading of the diffuse erythematous network so that at times it was barely visible (fig. 13).

An attempt was made to obliterate the dilated venules above the knees previously described. The area shown in figure 12 on the outer side of the right thigh was treated with injections of from 0.2 to 0.3 cc. of the 1:3,000 solution of

Fig. 12 (case 3).—Dilated venules on the outer side of the right thigh before treatment (Oct. 5, 1935).

venom right alongside of one of the dilated veins at weekly intervals. Some of the veins were treated from three to five times. By November 1 the vessels which remained had become resistant to the therapy so that the concentration of the solution had to be increased to 1:1,000. This proved efficacious. Amounts of from 0.1 to 0.2 cc. were injected as before. The marked difference in the

appearance of the lesions can be seen by comparing figures 12 and 14. At the end of November a 1:1,000 solution failed to cause a local ecchymosis.

It is of interest to note that the patient reported at the end of December that her last two menstrual periods lasted only five days and that the flow was moderate. Venom tests made on all regions of the body at that time were persistently negative. The patient is still receiving two injections of the 1:3,000 solution

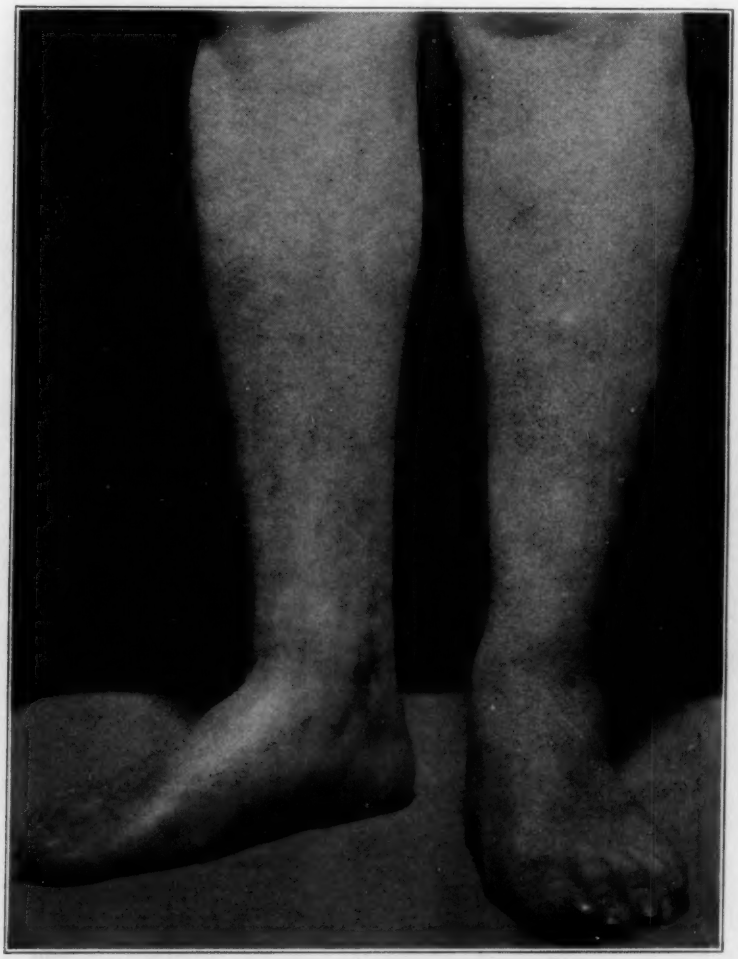

Fig. 13 (case 3).—Photograph showing marked improvement resulting from venom therapy (Feb. 22, 1936).

weekly, although treatment was given somewhat irregularly. At present she shows just faint shadows of the irregular serpiginous erythematous network on the lower portion of the legs. They can be made more prominent by exposure to heat. The angiomatous puncta have not been seen since their first disappearance during the early part of the treatment. With the clinical improvement the pain in the legs and the swelling of the ankles have disappeared.

This case illustrates clearly the possible value of the venom therapy in cutaneous diseases resulting from certain types of vascular disturbances. It also opens up the possibility that venom in definite dilutions or even venoms other than those used because of their specific endothelial action can be used for the obliteration of dilated venules. It must be remembered, however, that the more normal the vessel, the greater its resistance to the hemorrhagin in the venom.

Fig. 14 (case 3).—Appearance of area shown in figure 12 after local injection of moccasin venom (Dec. 14, 1935).

COMMENT

The mechanism of purpura formation is at present under investigation by many experimenters because of the stimulus given this subject by recent discoveries.

The literature is filled with experimental and clinical observations on the uses of vitamin C, especially with regard to its use for the control of various hemorrhagic conditions (Molitch,[16] Göthlin,[4] Dalldorf and

16. Molitch, M.: Subclinical Scurvy in Children: Application of Capillary Resistance Test, J. Lab. & Clin. Med. **21**:43, 1935.

Russell [17]). These authors have stressed the value of vitamin C in raising capillary resistance to intracapillary pressure. Hess and Wolbach and Howe [18] were the first to suggest that the interendothelial substances were closely related to vitamin C.

Our clinical experiences with the intravenous injection of vitamin C in doses of 200 mg. three times a week in treatment of patients with thrombocytopenic purpura haemorrhagica and Osler's disease have shown that it is certainly not similar to the venom in its action. We have been unable to observe any clinical or hematologic improvement in a patient with thrombocytopenic purpura haemorrhagica resistant to venom therapy. In another patient showing clinical but not hematologic improvement as a result of venom therapy there was no rise in the number of platelets after injections of vitamin C. In a patient with Osler's disease, in whom venom therapy had caused a marked diminution of the bleeding, intravenous injections of vitamin C seemed to have no additional beneficial effect. It should be mentioned that tests for vitamin C with dichlorophenolindolphenol were negative with the dilutions of venom used.

Bedson [19] has shown in experiments with animals that the diminution of platelets alone could not be held responsible for the production of experimental purpura. He expressed the belief that an endothelial toxin must be present which caused rhexis of the capillary walls, initiating hemorrhage.

Clark [20] by direct observation of the capillaries in rabbits' ears by means of a window was able to demonstrate that inflammation caused bulging and disintegration of the endothelium. Abell [21] showed that solutions of phosphate in sufficient concentrations and possibly metabolic products could cause damage to the endothelial cells with rupture of the capillaries and hemorrhage.

Landis [22] in his outstanding work, in which he measured directly the blood pressure of arterial and venous capillaries (before and after

17. Dalldorf, G., and Russell, H.: The Effect of Cevitamic Acid Injections on Capillary Resistance, J. A. M. A. **104**:1701 (May 11) 1935.

18. Hess, A. F.: Recent Advances in Knowledge of Scurvy and Antiscorbutic Vitamin, J. A. M. A. **98**:1429 (April 23) 1932. Wolbach, S. B., and Howe, P. R.: Intracellular Substances in Experimental Scorbutus, Arch. Path. **1**: 1 (Jan.) 1926.

19. Bedson, S. P.: Blood Platelet Antiserum: Its Specificity and Rôle in Experimental Production of Purpura, J. Path. & Bact. **25**:94, 1922.

20. Clark, E. R.: Growth and Development of Function in Blood Vessels and Lymph Glands, Ann. Int. Med. **9**:1043, 1936.

21. Abell, R. G.: Effect of Buffered Phosphate Solutions upon the Thin Layer of Living Vascular Tissue in Moat Chambers Introduced in the Rabbit's Ears, Anat. Rec. **64**:51, 1936.

22. Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev. **14**:404, 1934.

the formation of a capillary loop) has given a great insight into the mechanism responsible for the formation of purpura due to increased intracapillary pressure.

It would be of prime importance for the study of capillary disease if the active principle of the venom were to be isolated and if the exact mechanism of the action of the venom could be established. Previous experiments seemed to indicate that the therapeutic principle in moccasin venom cannot be identified with the established toxic components of the venom, such as neurotoxins, hemotoxins and hemorrhagins.[23] It has been shown that the venom did not act as a foreign protein in the broad sense of the term since identical concentrations of venoms of individual moccasin snakes had different therapeutic potencies. The addition of normal horse serum in some instances has interfered with the antihemorrhagic action of the venom.[24] All these observations indicated a definite therapeutic component.

The mechanism of the action of venom is as yet poorly understood. The antihemorrhagic effect is not due to the formation of circulating substances such as antivenin.[25] The weight of evidence seems to indicate that the action is directly on the capillaries, making them resistant to rhexis. The use of moccasin venom for therapeutic purposes is based on the observation that after an incubation period it made rabbits resistant to the Shwartzman phenomenon (an experimental purpura due to vascular toxins [6a]).

There is clinical evidence which supports the contention that the venom acts on vessel walls, making them resistant to hemorrhage. In a number of patients with Osler's disease some of the telangiectases of the mucous membranes were seen to diminish or disappear entirely. After prolonged periods of treatment with venom a similar clinical result could be observed in a patient with angioma serpiginosum. In patients with thrombocytopenic purpura the effect on the vessels was indicated by a reversal from a positive to a negative reaction to venom in spite of the persistently low platelet count. This clearly indicated an increased capillary resistance, since there was not enough antihemorrhagin formed in the blood of these patients to influence the test in any way. Also patients with symptomatic purpura with a normal blood

23. Peck, Samuel M.: A Refractory State as Concerns the Shwartzman Phenomenon: I. Observations on Potency of Individual Venoms, J. Immunol. **25:** 447, 1933.

24. Peck, Samuel M.: A Refractory State as Concerns the Shwartzman Phenomenon: II. Inhibition of Refractivity Producing Factors in Moccasin Venom by Antivenin and Normal Horse Serum, J. Immunol. **27:**89, 1934.

25. Taylor, K. P. A.: Antivenin in Thrombocytopenic Hemorrhage: Importance of Bothropic Type, Am. J. Surg. **21:**285, 1933. Peck and Sobotka.[6a]

picture, a condition known as Schönlein-Henoch's disease, anaphylactic, endocrinal and orthostatic purpura have in many instances responded well to the venom therapy.

The venom test differentiated local from generalized types of purpuric manifestations. Patients with active purpura confined to the legs which was due to local causes showed a positive reaction only on the lower extremities. A generalized capillary fragility or toxicosis with purpuric manifestations located predominantly on the legs caused a reaction which was positive on all regions of the body tested.

Ordinary hemangioma of the face showed a negative reaction when 2 and 12 units of hemorrhagin were injected intradermally directly into the lesions. Similarly the small telangiectatic lesions of Osler's disease were resistant to the introduction of venom. This is an example of how the venom test differentiates nevoid lesions from pathologic changes in the vessels.

It was of interest to note that chronic discoid lupus erythematoides, even when extensive, gave a negative reaction to venom in the affected areas. On the other hand, the acute disseminating fatal variety, especially the group showing the changes in the vessels described by Baehr [26] and his associates, gave strongly positive reactions. More extensive investigation on the use of the venom test in various dermatologic conditions is now in progress and will be reported in a separate paper.

SUMMARY

A classification of purpuric and allied manifestations of the skin and mucous membranes from the clinical and the hematologic standpoint is presented.

Preliminary studies of the histology of purpura from the experimental and the clinical point of view are given.

The value of moccasin snake venom as a diagnostic, prognostic and therapeutic agent in these conditions is discussed.

ABSTRACT OF DISCUSSION

DR. JOHN H. STOKES, Philadelphia: The applause which followed the reading of this paper indicates that the members realize the value of the presentation. The authors are to be congranulated on their work, and the association is to be congratulated on the authors' membership. Unhappily, in recent years it has been true that some of the most fundamental advances in knowledge of cutaneous physiology and pathology have not been made by dermatologists. The field of vascular pathology especially has been reverting to general medicine through the default of dermatologists, and it is particularly gratifying to see some of them reclaiming part of their birthright.

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26. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation Usually Associated with Lupus Erythematosis and Endocarditis, Tr. A. Am. Physicians **50**:139, 1935.

One should emphasize also the value of the contribution in the field of method. One whose task it is to keep graduate students occupied in work of an advanced character in the field of dermatology soon realizes how serious is the paucity of methods for attacking problems of function in a fundamental way. One is constantly misled by the uncritical use of method and by the adoption of methods unsound in themselves and invalidated by controls applied by the next observer but overlooked by oneself. Dr. Peck and his co-workers have had national and international recognition for this contribution both to knowledge and to controlled and controllable method. When one realizes that practically everything that is now known about the function and pathology of cutaneous vascular disease was taught by the cardiologist Sir Thomas Lewis and the physiologist Krogh, one is proud and satisfied to welcome a dermatologist as a new authority in this field of method.

As I heard Dr. Peck talk, one or two illustrations of the ever present problem of controls in work such as this occurred to me. He has no doubt already covered the subject in full detail here and elsewhere. What steps are taken to secure uniformity of the venom after it is pooled? In the study of hormones a notable advance and a special effort have early been made in the isolation of a pure substance or pure substances. To what extent has Dr. Peck been able to foreshadow such a development, and what assistance has he had in projecting such a research? Is he satisfied that the loss of elastica precedes the purpura, or does it follow it? One knows how sensitive the elastica seems to be to cellular and pressure invasions and how obscure are the causes of atrophy, and it would be easy in a problem of this sort to put the cart before the horse.

One pictures, of course, remarkable possibilities for the clinical application of the work of Dr. Peck and his associates. How does he feel about its applicability to the problems of postarsphenamine purpuric syndromes? Does he feel that it has prognostic significance in determining the eligibility of patients who have shown thrombocytopenic and leukopenic reactions for further arsenical treatment? To what extent are purpuric reactions an expression of direct vascular injury, and to what extent are they an indication of hematopoietic injury? Is it possible that the resistance of the vascular system to injury by drugs can be artificially raised in patients who have shown a vascular sensitiveness, so as to permit the use of drugs like the arsphenamines and the aminopyrine-phenobarbital combinations? When one recalls the loss to science and to dermatology that resulted from the death of Bruno Bloch one wonders whether it is possible to develop a method whereby a predisposition of the hematopoietic and vascular mechanism to certain changes might be recognized by test in advance of catastrophe in persons who for one reason or another are compelled to use the coal tar analgesics and sedatives. These are some of the questions which beset a mere clinician like myself—questions which Dr. Peck has no doubt already envisaged and is preparing to answer.

Dr. J. Frank Fraser, New York: The best test of scientific knowledge is to know what to do with it, and I think that Dr. Peck has clearly pointed the way in which one should proceed in the application of this knowledge. He has shown the beginning of the simplification of classification in vascular diseases of the skin. Experimental purpura has been divided into two main classes—that in which the mechanism of the hemorrhage is diapedesis, and the toxic, in which the mechanism is rupture of the vessel walls.

In regard to the importance of the rôle played by the elastic tissue, fragmentation of elastin, together with diminution, in some cases was the usual histo

logic change, but in one case the elastic tissue was well maintained. I wish to ask the authors' views on the pathogenesis of these observations. In regard to the venom, there can be little doubt as to its usefulness, not only as a therapeutic agent but also as an aid in diagnosis and prognosis in cases of vascular diseases.

Dr. Eugene F. Traub, New York: Some months ago Dr. Peck supplied me with some of the venom he uses and gave me the details of his method so that I have had an opportunity of doing a considerable number of tests and of observing the result of treatment in some cases.

It is seldom that in a single procedure one is given a method for studying the etiology and histology of an obscure group of diseases, the differential diagnosis of numerous groups of diseases and individual disorders, their prognosis and, what is perhaps most important, a new avenue of approach in the treatment of those conditions. Such is, nevertheless, the case in this instance. I should like to stress the value of the venom test in a number of particular types of disorders. For instance, the various vascular nevi or congenital vascular anomalies can be distinguished from vascular changes observed in inflammatory conditions and tumor formations such as those in Kaposi's sarcoma, because in cases of the latter diseases the reaction to venom is positive while in those of the nevi a negative reaction may be expected. In cases of lupus erythematosus of the chronic disseminated type, in which the prognosis is generally favorable, a negative reaction may be expected, regardless of on what part of the body the test is performed, while in cases of the acute disseminated and frequently fatal type of the disease, a positive reaction may be expected, regardless of the site tested. In cases of purpura, as the authors have pointed out, the reaction to the venom tests helps the clinician to separate and classify conditions belonging to this confused group, and, what is more important, the result of the test is a guide as to the prognosis. It is also an earlier and more accurate indicator in most instances than the platelet count as to changes in the patient's condition. For instance, patients with chronic purpuric lesions associated with a positive reaction to the venom test should be given treatment with venom, regardless of the blood picture, an early and favorable outcome being generally indicated by a return of the reaction to negative. In cases of vascular diseases of the extremities, such as Majocchi's and Schamberg's disease, angioma serpiginosum, dermatitis haemostatica and the fine varicose venules most frequently seen on the legs of women, not only should the test be performed, but treatment with venom should be given, as it is frequently successful. I have observed three or four patients with dermatitis haemostatica with what appeared to be some patches of permanent iron pigment deposit in the skin in whom the condition cleared up almost entirely as a result of treatment with venom, and I have also seen improvement of these fine varicose venules in one patient. It is desirable to attempt treating with venom in as many varieties of vascular disease as possible; as the method is new as yet, no one can tell how big the field may be in which it may be successful.

One of the most important points which I think should be mentioned is that neither the test nor the treatment seems to offer a hazard of any kind. No unpleasant reactions are to be expected, the worst that may occur being a slight local swelling which disappears without any special treatment. When the full paper is published, the true value and extent of the work may be better appreciated.

Dr. Fred D. Weidman, Philadelphia: To the pathologist there are three factors in the development of hemorrhage: (1) pressure within the blood vessel; (2) degeneration or other weakening lesions of the walls of blood vessels, both of which have been emphasized by the authors, and, (3) lack of support from

outside. In connection with the latter, at necropsy in cases of anemia one observes hemorrhages in the skin, in mucosa and on serous surfaces (pericardium), i. e., in positions where there is not a bulk of solid tissue outside the blood vessel to support it, and I dare say that the elastic tissue degeneration which was mentioned in the authors' cases would fall under that head, the "outside" tissue no longer supplying support to the blood vessel wall.

I do not quite know the composition of the venom which the authors used, and I wonder whether it contains any of the pathogenic substances which are contained in cobra venom. In cobra vaccine there is an efficient antivenin—meaning antibodies, and I am curious to know whether there is any corresponding relation, immunologically speaking, between the venom which the authors used and that which is present in cobra vaccine. I also wonder whether changes similar to those reported by the authors would occur in the skin as a result of inoculation of cobra venom.

I am also curious to learn whether the venom induces any changes, however slight, in the bone marrow or in the thrombocytes. I realize that the patients whom the authors studied have not come to necropsy, but if one is to follow this subject in all its details, as I know the authors will, the study should include examination of the bone marrow.

Dr. Samuel M. Peck: The toxicity of moccasin venom is not uniform. In a published paper (A Refractory State as Concerns the Shwartzman Phenomenon. Observations on Potency of Individual Venoms, *J. Immunol.* **25**:447 [Nov.] 1933) I have brought out this point. It was for this reason that a method had to be devised to titrate the hemorrhagins in the venom. Pooled venom is used for the test. At icebox temperature no deterioration takes place for many months.

At the present time we are investigating the question of vascular toxicity of arsphenamine. This work is being carried out on the service of Dr. Fox at the Bellevue Hospital, and I think that it is promising and may lead to valuable information. It is too early to state definitely whether one can foretell if in certain cases damage to the vessel walls will result from the arsenicals.

The aminopyrine group does cause purpuric eruptions, and the reaction to the venom test adequately parallels the clinical symptoms and in addition accurately foretells improvement by a reversal from a positive to a negative reaction.

A great deal more work must be done in the purpura group before detailed questions about the elastic tissue can be answered. The result of our investigations seems to indicate strongly that the elastic tissue plays an important rôle in the formation of purpuric eruptions; it certainly does so on the dependent portions.

Dr. Rosenthal and Dr. Erf have thoroughly investigated the question of the bone marrow by means of sternal punctures, and they have presented a paper on the subject in the last few months. Certainly we have found that this procedure when carried out carefully has no dangerous sequelae and can be used in the outpatient department.

In the test I am, of course, titrating the hemorrhagins in the venom, and the test itself depends on the effect of these hemorrhagins on the vessel walls.

Cobra venom does not give a positive reaction because while it is rich in hemolysins it is poor in the so-called hemorrhagins.

The question of chemical fractionation is under investigation, and I have been fortunate enough to obtain a grant so that a good chemist is available to assist me in this work.

HERPES ZOSTER AND HERPES SIMPLEX

REPORT OF A CASE IN WHICH BOTH APPEARED SIMULTANEOUSLY; ANALYSIS OF THEIR ETIOLOGY

WILLIAM H. GOECKERMAN, M.D.

AND

L. F. X. WILHELM, M.D.

LOS ANGELES

Despite extensive literature on both herpes zoster and herpes simplex, there seems to be little accurate knowledge as to the exact nature of these conditions. This becomes apparent when one reviews the writings of various authors and one's own experience in a critical manner. The case reported here was unique in our experience, as herpes zoster and herpes simplex occurred simultaneously and seemingly as the result of the same infection. While this may have been coincidence, we did not wish to accept it as such owing to the rather striking course of events. The occurrence gave rise to much speculation on our part and caused us to review the literature in the hope of crystallizing our conception of the nature of these dermatoses. It must be said frankly that the result of that review was not satisfactory to us. It is offered, nevertheless, in the hope of stimulating sufficient discussion to bring out the preponderating opinion of the present day.

CASE REPORT

Mrs. V. L., aged 40, had an irrelevant history; she stated that she had never had any cutaneous eruption, and she emphatically asserted that she never had anything akin to the present lesions. She was an intelligent person, a teacher, and her statement seemed reliable. She was seen on June 11, 1935. At that time she presented grouped vesicular lesions on the right side of the face and neck, involving the lower lip, tongue, cheek, fauces and cervical region down to the clavicle. There was satellite adenopathy of the right side. The vesicles had an erythematous infiltrated base and were painful and tender. Covering practically the entire vulva bilaterally was a profusion of superficial painless vesicles, which had appeared at approximately the same time as the lesions in the cervical region. The eruption had been preceded for about two weeks by indefinite aches, malaise and a daily rise of temperature of 2 or 3 degrees F. The patient had felt sufficiently ill to remain in bed most of the time, but there had never been any severe prostration. The eruption, the fever and the malaise were present for about three weeks. The pain in the cervical region persisted for approximately one additional week. After that the patient seemed perfectly well. Treatment

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had consisted of rest in bed, calamine lotion locally and acetylsalicylic acid by mouth. It seemed as though the process ran a self-limited course. The routine laboratory tests, including the Wassermann test of the blood, were negative.

Comment.—There can be little doubt that in this case some infectious process was present. The malaise, fever, course of several weeks with spontaneous involution and recovery point to infection. Not so certain is the common etiologic factor of the herpes zoster and the herpes simplex. If this assumption, a fairly logical one, is valid, however, one may conclude that at least occasionally the same virus may produce both types of lesion.

REVIEW OF THE LITERATURE AS TO THE ETIOLOGY OF HERPES ZOSTER AND HERPES SIMPLEX

The literature on herpes zoster and herpes simplex is enormous. As nothing can be gained thereby for our purpose, no effort will be made to cite the complete literature; we shall merely evaluate the opinions expressed by various authors that seem to fit our purpose of obtaining a better understanding of the etiology of these two conditions. If one reads the various textbooks on dermatology, it is easy to conclude that there is a multiplicity of etiologic factors. Apparently simple irritation of the peripheral nerves by sun rays, drafts of cold air, mild trauma or even friction may be responsible. Again, such an upset as simple indigestion, menstruation or mild diarrhea without systemic symptoms may be followed by herpes simplex. A food or a drug may cause the eruption. In striking contrast to such insignificant factors, a vicious infection, such as cerebrospinal meningitis, lobar pneumonia or malaria, produces an identical eruption in a large percentage of cases; and less often scarlet fever, diphtheria, influenza, typhus and typhoid is responsible for an outbreak. A similar array of causes is cited for herpes zoster. But the severe infectious diseases are less often associated with it. The one exception is possibly varicella.

To all this we can readily agree on the basis of our personal experience. However, an eruption so characteristic in appearance and behavior would seem to have a specific etiologic agent. Efforts have therefore not been wanting to demonstrate such an agent. While this has not been successful in regard to herpes zoster, it is apparently agreed that the virus of herpes simplex may be successfully inoculated into the cornea of a rabbit, and Greenbaum and Harkins [1] stated that the virus may be transmitted to laboratory animals not only by the content of vesicles but by the spinal fluid, saliva and blood serum. It would hardly seem feasible to assume that a herpetic eruption occurring

1. Greenbaum, S. S., and Harkins, M. J.: Experimental Studies of Immunity in Herpes Simplex, Arch. Dermat. & Syph. **11**:789 (June) 1925.

monthly in association with menstruation or developing as a result of ingestion of wholesome food or of a drug nontoxic in the dose given would produce a vesicle the content of which would set up a vicious process in a rabbit. McFarland,[2] who was of the opinion that herpes simplex and herpes zoster have the same etiology, suggested that a virus akin to that seen in the bacteriophage phenomenon may be the cause and explain some of the problems. Schamberg [3] pointed out that there are similarities but also dissimilarities between herpes simplex and herpes zoster. There is a tendency to recurrence in herpes simplex but not in herpes zoster. Histologically, there is a definite similarity. This similarity could be due to the involvement of similar structures by different noxae, as it is known today that identical histologic pictures may be produced by the bacillus of tuberculosis, Spirochaeta pallida and other organisms.

The immunologic behavior is not so readily explained. Rosenow and Oftedal [4] in their well known work expressed the opinion that there is an elective affinity between the streptococcus and other bacteria and the ganglions and posterior nerve roots in cases of herpes zoster. That this phenomenon may be a factor cannot be denied, but that it fully explains the etiology seems unlikely, as one attack of herpes zoster is the rule, whereas were the disease due entirely to an affinity between the micro-organisms and the nerve structures invasions de novo should be common. If focal infection by a special strain of streptococcus were the answer, repeated attacks should be the rule so long as the focus remained in the body. If one were to admit a modified streptococcus to be responsible for poliomyelitis, encephalitis and chickenpox and herpes zoster to be due to an attenuated form of this virus, the tendency to development of immunity after one attack, even if mild, might be explained. It is known, however, that these diseases are not mutually protective. Youmans [5] reported a case of so-called herpetic fever with stomatitis in which the virus was isolated from the oral lesions and inoculated into the cornea of a rabbit. Attempts to isolate the virus from the blood and spinal fluid failed. The observations in this case seem to argue strongly in favor of a specific infectious agent as the

2. McFarland, A. R.: A Clinical Study of Herpes with a Review of Fifty-Eight Cases, New York State J. Med. **34**:637, 1934.

3. Schamberg, J. F.: The Nature of Herpes Simplex, with a Consideration of Its Diagnostic and Prognostic Significance in Various Infectious Diseases, J. A. M. A. **98**:746 (March 2) 1907.

4. Rosenow, E. C., and Oftedal, S.: The Etiology and Experimental Production of Herpes Zoster, J. Infect. Dis. **18**:477, 1916.

5. Youmans, John B.: Herpetic Fever with Stomatitis, South. M. J. **25**: 228, 1932.

cause. The fact that the virus could not be isolated from the blood or spinal fluid does not militate against this conception. The specificity of the etiologic agent in some cases seems further confirmed by the frequent association of herpes zoster and varicella. For this conception it matters not whether an attack of herpes zoster is associated with a generalized eruption of varicella vesicles, whether other members of the family have varicella after an attack of herpes zoster or whether an attack of herpes zoster develops during an epidemic of varicella. To deduce from this, however, that the virus responsible for varicella is always the cause of herpes zoster is probably not justifiable. It is a striking fact that the histologic picture in cases of herpes zoster and herpes simplex is characteristic and that it resembles more closely the changes in varicella than those in any of the other vesicular diseases, no matter what the clinical features in a given case may be.[6]

While this is naturally suggestive of a common etiologic factor, especially in cases of diseases so different in their clinical manifestation, it is known that different micro-organisms may produce identical histologic changes. We are inclined to attribute this similarity to the method of trauma inflicted on special anatomic structures rather than to any specific characteristics of the virus.

In certain cases herpes simplex has been proved to be due to a specific virus inoculable into the cornea of a rabbit. Surprisingly, this is not true of herpes zoster, and yet on first blush the infectious nature of herpes zoster seems more apparent than that of herpes simplex. It is usual to find associated with the former some malaise, moderate fever and satellite adenopathy. In addition to this, if an examination of the spinal fluid is made, some change is usually observed. Schuessler[7] systematically examined the spinal fluid in eighteen cases of herpes zoster and found changes in sixteen. The pressure was increased in the majority, and neuralgia was relieved by draining off some spinal fluid; this was true also in cases in which the pressure was not increased. Schuessler treated the eruption by intracutaneous inoculations of spinal fluid and found the treatment valuable. Schmidt[8] successfully treated recurrent herpes simplex by vaccination with vesicular fluid. This observation also seems to point to the infectious nature of both types of herpes, but only in a certain number of cases.

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6. Gans, Oscar: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1927, vol. 2, p. 51.

7. Schuessler, D.: Ueber die Liquorveränderungen beim Zoster, Dermat. Wchnschr. **100**:381 (April 6) 1935.

8. Schmidt, F. R.: Vaccination for Herpes, Arch. Dermat. & Syph. **32**: 106 (July) 1935.

SUMMARY

In the case reported here the condition seemed to be on an infectious basis. We believe that the case suggests that herpes zoster and herpes simplex may be due to the same virus and that the difference in the clinical manifestation is the result of different points of attack on anatomic structures. We should like to assume that in the cases of herpes zoster the ganglions and larger nerve trunks bear the brunt whereas in those of herpes simplex the superficial nerves chiefly are involved. We do not believe that any deduction can be drawn from our case as to whether the virus is carried by the blood stream or whether it travels along the nerve elements, although we are inclined to favor the former theory. While our case points to an infectious nature of herpes zoster and herpes simplex, there is much evidence that in other cases any type of inflammation of the spinal ganglions and nerve fibers may produce a herpetic eruption. We favor the opinion that there are multiple etiologic factors for both herpes simplex and herpes zoster and that therefore the eruption called herpes is merely a symptom, the clinical characteristics of which are determined by the anatomic point of attack. Evidently the causative factors may be infectious, chemical, allergic, or even metabolic or endocrine. The subtle conception that all herpes simplex is infectious and becomes manifest clinically at intervals as a result of some intercurrent factor does not seem to us to harmonize with common experience.

CONCLUSIONS

1. The same etiologic agent may produce either herpes simplex or herpes zoster.

2. Bacteria of various types may produce herpes simplex and herpes zoster.

3. In many cases herpes zoster or herpes simplex may be due to a noninfectious agent.

4. The clinical and the histologic picture are probably determined by the anatomic involvement rather than by the nature of the irritant.

5. A focus of infection is more likely to be a causative factor in herpes simplex than in herpes zoster.

6. The modified virus of poliomyelitis or varicella is probably not responsible for herpes in all cases.

7. The theory that there is a specific causative agent in all cases of herpes simplex or herpes zoster cannot be accepted.

727 West Seventh Street.

ABSTRACT OF DISCUSSION

DR. CHARLES M. WILLIAMS, Stonington, Conn.: This paper interests me because I have just recovered from an attack of herpes zoster and have more respect for the disease than before. It seems to me herpes simplex is an infection caused by a virus which once implanted remains implanted, and I think that recurrent attacks, which are the rule rather than the exception, are caused by any of a multiplicity of agents, such as a common cold, pneumonia or any factor which lowers the resistance of the body. It does not seem to me that herpes simplex, considered as a disease caused by a virus, is caused by the same virus as herpes zoster, for the following reason: In herpes simplex recurrent attacks are the rule; the eruption does not necessarily occur in the same place, but attacks develop at frequent intervals. In herpes zoster as a rule one attack protects against recurrent attacks. It seems to me that this difference is rather against the assumption that the two conditions are caused by the same virus.

I think that in discussing herpes zoster the first thing to do is to agree on a definition. Should this name be applied to every disease that is zoniform? I think not. It is true that various drugs, notably arsphenamine, may produce an eruption that is clinically similar to herpes zoster. Unquestionably the causative agent acts on the spinal ganglions and produces the eruption. I think that the conception of the disease would be much clearer if the name were limited to the specific infectious disease producing the clinical signs with which dermatologists are familiar. The depression which follows zoster has not been sufficiently emphasized and may be severe. In my own case the pain and the physical signs were not great, but the malaise and depression were pronounced, and it took me two years to recover from the attack. A friend reported the same observation in his case; it took him two years to get back to normal. Another friend became delirious and has never completely recovered; in his case the mental symptoms were particularly severe. Last year I heard of a farmer who after suffering for seven weeks from herpes zoster died apparently as the result of the disease.

I wish to emphasize the severity of the mental and nervous symptoms, not including the pain, which may follow herpes zoster. I think one should consider these two diseases as being produced by an ultramicroscopic virus, but not by the same variety of virus, and I believe that the term zoster should be limited to the acute disease.

DR. M. H. EBERT, Chicago: Some years ago when this question was much discussed in the literature I undertook a series of experiments with inoculation of the virus of herpes simplex in animals and was successful. The age of the lesion is important. Material from a lesion one or two days old is most successfully inoculated. The animals used were rabbits, guinea-pigs and dogs. In the rabbits I also succeeded in producing the encephalitis which is described as being associated with the condition, and I was able to produce serial inoculations in all the animals. When I began this investigation I felt that perhaps there was an error, that material from other vesicular and bullous eruptions on the skin might be used and that a virus which was commonly present and had nothing to do with the herpes simplex but was only incidental might be the cause of the so-called herpetic keratitis. I performed experiments on these animals with material from pemphigus bullae and from lesions of multiform erythema, of dermatitis herpetiformis, of eczema and of other vesicular eruptions, and obtained no results; hence I was compelled to decide that the virus of herpetic keratitis was not present in various vesicular and bullous eruptions.

I think the zoster problem is intriguing, for the histologic picture in early stages of herpes zoster is known to be identical with that of herpes simplex. The multinuclear cells, the rounding up of the chromatin at the nuclear membrane and the eosinophilic inclusion bodies are present in both. These changes are present in the cornea of the rabbit or the guina-pig after inoculation. It would seem that inoculation with material in which these changes are present should produce "takes," but I was unsuccessful and have never heard that any one has been successful in producing herpetic keratitis with virus from vesicles of herpes zoster. I felt that the material was present in the enlarged lymphatic glands which accompany herpes zoster. If these glands are removed and the material is ground up and inoculated into the eye, brain or testicles of animals, the results are also negative. In attempting to recover the virus of herpes zoster one is handicapped by the fact that the initial lesion is in the nerve ganglion and that it is impossible to get the virus when it might be inoculable. I am thoroughly convinced that the two diseases are of entirely different type—that herpes zoster as well as herpes simplex, is a virus disease, but that so far the virus of herpes zoster has never been demonstrated.

Dr. Paul E. Bechet, New York: I am particularly interested in the pathogenesis of these two dermatoses because I have suffered from herpes facialis for years, attacks occurring several times each year. In my case it seems that the attacks almost invariably precede or accompany gastro-intestinal irritation or severe exposure to actinic rays. While Gruter, Lipschutz and other investigators have reproduced herpetic lesions on the corneas of animals, I believe that until more definite evidence can be produced the old theory of focal irritation still holds good. The evidence of a specific virus in zoster is more convincing, as epidemics of zoster have been reported, specifically by Sachs. Rosenow and Oftedal produced lesions resembling zoster in animals by injecting material isolated from the tonsils of patients suffering from zoster. The association with varicella is significant, as is the occasional appearance of a varicella-like eruption during an attack of zoster. I have always believed that the two diseases are dissimilar, etiologically and symptomatically.

Dr. Jacob H. Swartz, Boston: I wish to say a word about the treatment of herpes zoster, particularly of involvement of the eye. Dr. Gunderson, of the Massachusetts General Hospital, has been using convalescent serum successfully in cases of this condition. Within twenty-four hours after the injection there is definite improvement. I also believe that this treatment points toward the infectious element in herpes zoster.

Dr. Charles M. Williams, Stonington, Conn.: I neglected to mention that in my youth I suffered from chickenpox. It did not protect me against herpes zoster.

Dr. William H. Goeckerman, Los Angeles: One of the objects of the paper was to bring out the present day ideas in regard to these cutaneous manifestations. I think the discussion has brought out the opinions, and, as was expected, they are somewhat at variance. I know the most modern conception is that herpes simplex is essentially a specific virus disease which is inoculable in animals, but this theory has not been accepted for herpes zoster. The case reported here suggests strongly that the two conditions may occasionally be caused by the same virus. Clinical study has convinced me that herpes simplex is not due in all instances to an infectious agent. I believe that, as is the case with studies of many other diseases, experiments with animals will not fully explain the etiology.

FIXED DRUG ERUPTIONS

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We believe that the term fixed drug eruption as first applied and interpreted by Brocq is not always employed in the original sense. As a help to a better understanding of such eruptions we are restating the definition of the term fixed so far as it applies to drug eruptions. We submit also a compilation of the different types of fixed eruptions that have been reported, the various drugs and other agents considered responsible for them and some comments on the pathogenesis of such manifestations.

HISTORICAL NOTES

Soon after 1885, when antipyrine came into use, several observers called attention to eruptions caused by this drug. One type noted was peculiar in that it recurred at the previously affected areas of the skin whenever antipyrine was again ingested.

Brocq [1] after observing several cases, designated such cutaneous manifestations as fixed. His description may be summarized as follows: The cutaneous manifestations appeared as round or oval apparently edematous plaques from the size of a coin to that of a palm recurring on various parts of the body and accompanied by an itching or burning sensation. The patches were dusty red at their onset and showed definite borders. At times these lesions progressed to form bullae. Desquamation or crusting (after the bullous lesions) appeared as the eruption faded, leaving a pigmentation of variable shade and duration in the areas affected. A special characteristic of the eruption was the tendency to relapse and recurrence of the lesions in situ.

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Read before the Section on Dermatology and Syphilology at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 14, 1936.

1. Brocq, L.: Éruption érythémato-pigmentée fixe due à l'antipyrine, Ann. de dermat. et syph. **5**:308, 1894.

Ehrmann,[2] Mibelli,[3] Apolant[4] and others made further studies of fixed eruptions caused by antipyrine, and thus the terminology became established. Aminopyrine (dimethylaminophenyldimethylpyrazolon; pyramidon), introduced about 1899, as well as other compounds of antipyrine that came into use later were also found to produce similar eruptions at times.

DEFINITION OF THE TERM FIXED DRUG ERUPTION

According to Brocq, Ehrmann, Mibelli, Apolant and others, the term fixed, as its name may imply, does not refer to the duration of the cutaneous lesions. It does not refer necessarily to the residual pigmentation that often appears but signifies the repeated recurrences with a flare-up in the previously affected (hypersensitive) areas of the skin. Accordingly, the eruption may be fixed even when evanescent (urticarial), provided there exists a tendency to recurrence in the previously affected site, irrespective of whether the pigmentation noted after the more inflammatory lesions appears or not. While the pigmentation following numerous attacks of a fixed eruption may be of long standing, it ultimately disappears provided the use of the drug is discontinued. This pigmentation is due to melanin, is dopa positive[5] and should not be confused with the pigmentation that may also appear in patches on various areas of the skin after the use of various metallic preparations (arsenic, bismuth, gold and silver). Argyria and pigmentation from other metals appear insidiously and are more or less lasting even when the use of such a drug is discontinued. They are principally due to an increased deposit in the skin of the respective metal or its compound. Although metallic pigmentations may be accompanied or preceded by some form of dermatitis, there is no sudden flare-up in the pigmented areas each time the offending drug is used again.

THE COMMON TYPES OF FIXED ERUPTIONS

The erythematous (and bullous) plaques of various sizes and locations followed by pigmentation are the common types of fixed lesions seen. The fixed eruption from the various arsphenamines is at times transitory (urticarial), but it often assumes the characteristic fixed erythematous type already referred to as resulting from antipyrine and described as

2. Ehrmann, S.: Das Antipyrinexanthem, in Mraček, F.: Handbuch der Hautkrankheiten, ed. 4, Vienna, A. Hölder, 1902, vol. 1, p. 654.

3. Mibelli, V.: Ueber die fixen Antipyrinerytheme, Monatsh. f. prakt. Dermat. **26**:533, 1898.

4. Apolant, H.: Zur Pathogenese der localisierten Antipyrinexantheme, Dermat. Ztschr. **6**:67, 1899.

5. Weiss, R. S., and Kile, R. L.: Unusual Phenolphthalein Eruption: Report of a Case, Arch. Dermat. & Syph. **32**:915 (Dec.) 1935.

caused by phenolphthalein [6] and the barbiturates.[7] In addition to these drugs, acetylarsan, mapharsen, tryparsamide, cinchophen, mercury, quinine and acriflavine hydrochloride (trypaflavine) are also reported as causing the common type of fixed eruption. In one instance mild mercurous chloride (calomel) and mercury bichloride, both inorganic compounds, were responsible (table).

The fixed eruptions may start as any of the polymorphous types of erythema produced by drugs, i. e., as morbilliform or scarlatiniform erythema or as eruptions of the erythema multiforme type, but instead of their disappearing entirely, as the latter usually do, some residual pigmented patches may remain. These residual lesions may flare up and subsequently recur, and once they have done so, they often continue to participate in future outbreaks.

Fixed lesions caused by drugs also appear in the mouth and on the genital and perianal regions. In these locations they may appear as local edematous or erythematous patches, but most often they are vesicular or bullous (pemphigoid) lesions which break, leaving an erosion. The mucosal eruptions may accompany the surface cutaneous lesions but may be present without them. The characteristic erythematous and bullous type may also appear in the periungual and subungual areas of the fingers [8] and of the toes. Disturbance in growth of the nail has been observed in certain cases of these conditions. The bullous type of fixed lesion of itself should not cause any permanent damage to the skin. Ulcerations and scarring may follow in rare instances, and this raises the question of a local secondary infection as a complicating cause.

While fixed eruptions are likely to recur and lesions appear in the previously involved areas when the drug is subsequently administered,

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6. Abramowitz, E. W.: Erythema Multiforme Associated with Cutaneous Pigmentation (Melanin): Clinical and Pathologic Report of Five Cases, J. Cutan. Dis. **36**:11 (Jan.) 1918. Fox, H.: Erythema Perstans Following Ingestion of Phenolphthalein, ibid. **36**:252 (April) 1918. Wise, F., and Abramowitz, E. W.: Phenolphthalein Eruptions, Arch. Dermat. & Syph. **5**:297 (March) 1922.

7. (*a*) Wise, F., and Parkhurst, H. J.: Drug Eruptions from the Clinical Aspect with Special Reference to the Recent Medicaments, Arch. Dermat. & Syph. **6**:554 (Nov.) 1922. (*b*) Goldenberg, H., and Rosen, I.: Skin Manifestations Seen in a General Hospital, ibid. **14**:694 (Dec.) 1926. (*c*) Loveman, Adolph B.: Experimental Aspect of Fixed Eruption Due to Allurate, a Compound of Allonal, J. A. M. A. **102**:97 (Jan. 13) 1934. Meredith, F. L.: Reactions to Certain Barbital Derivatives, ibid. **102**:2099 (June 23) 1934.

8. (*a*) Beerman, H.: Phenolphthalein Eruption, Arch. Dermat. & Syph. **28**: 758 (Nov.) 1933. (*b*) Campbell, G. G.: Peculiar Pigmentation Following the Use of a Purgative Containing Phenolphthalein, Brit. J. Dermat. **43**:186 (April) 1931. (*c*) Ochs, B. F., in discussion on Rosen, I.: Drug Eruption, Arch. Dermat. & Syph. **26**:948 (Nov.) 1932. (*d*) Wise, F., and Sulzberger, M. B.: Drug Eruptions: I. Fixed Phenolphthalein Eruptions, ibid. **27**:564 (April) 1933.

it may also happen that new fixed spots develop, causing in time an increased generalization of the eruption. On the other hand, recurrences may become milder, or the eruption may altogether fail to appear when the use of the particular medication is resumed. There may also be some variation in the type of lesion with subsequent recurrences.[9] Relapses may also appear after the use of another drug.[7d]

THE LESS COMMON TYPES OF FIXED ERUPTIONS

These are essentially of two main types with various subdivisions, i. e., the urticarial (nodular) and the eczematous (erythematous scaly, follicular, papular, and vesicular [herpetic or erosive]) eruptions. References to such eruptions are cited under the various drugs listed in the table.

RARE FIXED EFFECTS

Naegeli, Jadassohn [10] and others noted instances of redness of one eye associated with tearing occurring regularly after each injection of arsphenamine. Milian [11] described a congestion of the inferior and outer quadrant of both ocular conjunctivae noted at times after the use of various arsenicals (atoxyl [monosodium salt of para-aminophenylarsenate], cacodylate [dimethyl arsenate], hectine [sodium benzosulfopara-aminophenylarsenate], arsphenamines and galyl [tetra-oxydiphosphaminodiarsenobenzene]). He considered this symptom as seen in its mildest form in the arsphenamine nitritoid crisis to be of importance as being possibly a premonitory sign of an impending arsenical erythroderma or purpura cerebri. Nicolas and his co-workers [12] called attention to a conjunctival reaction which followed each injection of bismuth hydroxide. Similar effects have been occasionally reported from phenolphthalein [13] and cinchophen (table). Conjunctivitis is more a feature of the generalized outbreak from the barbiturates [14] and nirvanol

9. Stokes: J. H.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1935, p. 488.

10. (*a*) Naegeli, O.: Ueber fixe Arzneiexantheme, Klin. Wchnschr. **6**:25 and 73, 1927. (*b*) Jadassohn, J.: Zur Kasuistik der Arzneischädigungen (Salvarsan, Quecksilber, Wismut), besonders über extracutane fixe Nebenwirkungen, Med. Klin. **21**:362, 1925.

11. Milian, G.: La conjonctivite arsénicale, Paris méd. **11**:303 (Oct. 15) 1921.

12. Nicolas, J.; Pétouraud, C.; Cuilleret, P., and Dugois, P.: Conjunctival Reactions After Each Injection of Bismuth Hydroxide, Bull. Soc. franç. de dermat. et syph. **41**:372 (March) 1934.

13. Stancanelli, P.: Dermatitie eritemato-pemfigoide recidivante de origine medicamentosa (fenolftaleina), Dermosifilografo **3**:10 (Jan.) 1928. Weiss, R. S.: Phenolphthalein Eruptions, Weekly Bull. St. Louis Med. Soc. **29**:421 (March 15) 1935.

14. Wise and Parkhurst,[7a] p. 553.

(phenylethylhydantoin).[15] The arsphenamines, phenolphthalein[16] and perhaps other drugs may occasionally cause a recurrent local pruritus in situ without any visible eruption. Various unaccounted-for recurrent subjective symptoms of the orificial mucosae may be due to the same cause.

The term fixed has been extended by Jadassohn[10b] to certain extracutaneous effects from drugs characterized by the recurrence in situ of symptoms in tissues other than the skin or mucous membrane. These appear as a peripheral nerve pain in the jaw or in the frontal or brachial area and have been known to be caused by repeated use of the arsphenamines and bismuth and mercury. Bargues[17] called attention to motor and sensory disturbances referable to the nerves of the brachial plexus and the hypoglossal and the chorda tympani nerve and to swellings of the jaw, recurring with each injection of neoarsphenamine, and he classed these manifestations with the local nitritoid crisis described by Milian. These effects are of a different pathogenesis than cinchonism or salicylism. The latter appear in nearly all persons if the dose of the respective drug is sufficiently large.

It is characteristic, according to J. Jadassohn, for the fixed effects, whether cutaneous or other, to make their first appearance in areas indistinguishable, both anatomically and functionally, from those that remain unaffected. It is usually not predictable, therefore, where the primary location of such a fixed eruption will be until after the first attack. Naegeli,[10a] however, called attention to instances in which an insect bite, a vascular nevus, a healed zoster and a previous cellulitis had apparently determined the location for the appearance of a fixed exanthem. Another report[18] shows that such lesions also appeared at the site of old cicatrices from burns. The entire question of the primary localization of fixed lesions and the elective location of other dermatoses is still too obscure to be answered definitely.

THE VARIOUS DRUGS REPORTED TO HAVE CAUSED THE DIFFERENT TYPES OF FIXED ERUPTIONS

Soon after arsphenamine was introduced a few authors observed the appearance of a recurrent urticarial erythema in situ following the

15. Atzrott, E. H. G.: Ueber Nirvanolvergiftungen, Therap. d. Gegenw. **61**: 375 (Oct.) 1920.

16. (*a*) Aubrey, G.: Toxic Effects of Phenolphthalein, Lancet **1**:1015 (May 7) 1932. (*b*) Hunt, E.: Toxic Effects of Phenolphthalein, ibid. **1**:905 (April 23) 1932.

17. Bargues, M.: Crises nitritoïdes localisées, Bull. Soc. franç. de dermat. et syph. **28**:244 (May 17) 1921.

18. Schreiber: Fixes Wismutexanthem, Dermat. Wchnschr. **93**:1642, 1931.

injection of this antisyphilitic agent. It was not until Naegeli,[19] in 1917, recalled the similarity of such eruptions to the fixed type reported by Brocq from antipyrine that this terminology came into use in reference to the arsenicals. Not only arsphenamine but its congeners have been noted to cause such lesions [20] (table).

*VARIOUS DRUGS REPORTED (alphabetically arranged) TO HAVE CAUSED A FIXED TYPE OF ERUPTION.**

Drugs	Comment
Acetophenetidin (phenacetin)	
Jadassohn, J.: Die Toxicodermien, Deutsche Klin. **10:** 137, 1905	Jadassohn stated that a circumscribed edema may develop
Acriflavine hydrochloride (trypaflavine)	
Ostrowski: Fixes Trypaflavinexanthem, Zentralbl. f. Haut- u. Geschlechtskr. **38:** 591 (Oct. 5) 1931	Ostrowski stated that after each injection there appeared palm-sized urticarial erythema in the vicinity of the site of injection
Antimony and potassium tartrate (tartar emetic)†	
Puente, J. J.: Toxidermia medicamentosa per fenolftaléina, Semana méd. **2:** 1156 (Oct. 17) 1929	In reporting a case of phenolphthalein eruption, Puente stated that he saw another patient who presented oval spots, some with atrophic dots in the center, on the trunk and limbs after having received injections of various drugs, such as potassium iodide, aminopyrine (pyramidon), antipyrine, acetylsalicylic acid (aspirin), sodium cacodylate, antimony and potassium tartrate (tartar emetic), solution of potassium arsenite (Fowler's solution), sulfarsenol and neoarsphenamine; congestion only resulted from antimony and potassium tartrate; neoarsphenamine also caused congestion followed by pigmentation; phenolphthalein was not tried
Antipyrine and Aminopyrine ‡	
Footnotes 1, 2, 3, and 4	
Arsenicals	
Acetylarsan (para-oxyacetylaminophenylarsinate of diethylamine)	
Sézary, A., and Gallerand, L.: Eruption érythémato-pigmentée fixe due à l'acetylarsan, Bull. Soc. franç. de dermat. et syph. **39:** 1113 (July) 1930	
Arsphenamines ‡	
Footnote 10*b*	
Bergmann, E.: Ein in loco rezidivierendes tuberöses Salvarsanexanthem, Arch. f. Dermat. u. Syph. **125:** 849, 1918-1920	Bergmann reported a tuberous fixed exanthem from arsphenamine; the patient had also taken potassium iodide and may have had a fixed iodide eruption†
Jessner, Max: Salvarsandermatitis, Zentralbl. f. Haut- u. Geschlechtskr. **6:** 227, 1922-1923	Recurrent weeping eczema of the feet occurred after treatment with arsphenamine
Ochinsky: Lokalisierte Salvarsandermatitis, Zentralbl. f. Haut- u. Geschlechtskr. **7:** 309, 1922-1923	Neoarsphenamine, silver arsphenamine and sodium arsphenamine caused a recurrence of palm-sized eczematous lesions to appear on the hands, genitals and thighs; mercury had also been given but was later excluded as a cause of the eruption
Footnotes 9, 10 and 11	

19. Naegeli, O.: Fixes Neosalvarsanexanthem und Adrenalinwirkung, Cor.-Bl. f. schweiz. Aerzte **47:**1291, 1917.

20. Thibierge, G., and Mercier: Taches érythémato-pigmentées à répétition "in situ" à la suite d'injections de novarsénobenzol, Bull. Soc. franç. de dermat. et syph. **26:**93 (April 10) 1919. Fuchs, D.: Fixe Salvarsanexantheme, Deutsche. med. Wchnschr. **45:**1276 (Nov. 13) 1919. Naegeli, O.: Ueber die Verwendung des Silbersalvarsans: fixes Silbersalvarsanexanthem auf früherem Herpes zoster, München. med. Wchnschr. **67:**1372, 1920. Grütz, O.: Ueber fixe Exantheme nach Altsalvarsan, Dermat. Wchnschr. **70:**305, 1920.

Drugs	Comment
Mapharsen	
Vero, F.: Fixed Eruptions Due to Arsenic: Report of a Case, Arch. Dermat. & Syph. **35**: 307 (Feb.) 1937	Vero reported the case of a Negress with various-sized and generalized deeply pigmented patches on the trunk; the lesion first appeared after injections of silver arsphenamine and later flared up after mapharsen was given; bismuth had no such effect.
	Illustration of a fixed arsphenamine eruption on the flexor surface of the forearm was given by Stokes;[9] the eruption, which was originally urticarial, recurred in situ with each injection and finally became a lichenified eczematous hyperpigmented plaque
Tryparsamide	
Boardman, W. P., in discussion on McCarthy, Francis P.: Dermatitis Due to Arsphenamine? Arch. Dermat. & Syph. **32**: 668 (Oct.) 1935	A woman exhibited a fixed eruption which became decidedly reddened after each treatment with tryparsamide
Kemp, J. E., and Menninger, W. C.: Fixed Eruption Due to Tryparsamide: Report of a Case, Am. J. Syph. & Neurol. **19**: 195 (April) 1935	The patient presented a fixed urticarial eruption
Robinson, Harry M.: Fixed Dermatitis Due to Tryparsamide, Am. J. Syph. **17**: 507, 1933.	A fixed dermatitis, the type of which is not mentioned, was present
Tolman, Myer, M., in discussion on McCarthy, Francis P.: Dermatitis Due to Arsphenamine? Arch. Dermat. & Syph. **32**: 667 (Oct.) 1935.	A fixed eruption occurred after administration of tryparsamide
Barbiturates ‡	
Footnote 7	Occasionally recurrent eczematous patches are caused by the barbiturates
Bismuth	
Footnote 12	Six times in succession each injection of bismuth hydroxide precipitated an acute conjunctivitis that rapidly subsided
Schreiber, footnote 18	An itchy papular eruption occurred on old scars from burns on the body and left thigh after administration of bismogenol (bismuth subsalicylate); the lesions recurred in the same scarred areas after administration of spirobismol (sterile suspension of quinine bismuth iodine and calcium sodium bismuthyl tartrate in acid-free oil)
Sweitzer, S. E.: "Fixed" Eruption Due to Bismuth, Arch. Dermat. & Syph. **30**: 306 (Aug.) 1934	Urticaria-like lesions and severe pruritus of the fingers, hands and arms and headaches occurred after each injection of bismuth subsalicylate in oil: soreness of the gums and slate-blue pigmented areas appeared over the body
Cinchophen (atophan) ‡	
Kissmeyer, A.: Et tilfaelde af atophanexanthem, Ugesk. f. læger **77**: 792, 1915; abstr., Arch. f. Dermat. u. Syph. **122**: 759, 1915-1916	Crown-sized partly confluent plaques of a bright red color on the face, edema of the eyelids, slight conjunctivitis and crusting of the lips reappeared each time, after even a small dose of atophan
Sokolowski, A.: Ein Fall von Ueberempfindlichkeit gegen Atophan, Zentralbl. f. Haut- u. Geschlechtskr. **38**: 635 (Oct. 5) 1931	Recurrent urticarial patch on the left palm, generalized pruritus and fever developed on two occasions after administration of atophan
Stiefler, Georg: Ein Fall von angioneurotischem Oedem nach Atophangebrauch, Med. Klin. **15**: 927 (Sept. 14) 1919	Edema of the eyelids, upper lip and labia developed; a similar eruption appeared four weeks later when the drug was again administered
Iodine ‡	
Bunch, J.: Case of Erythema Iris (Due to Potassium Iodide), Brit. J. Dermat. **25**: 64, 1913	Erythema multiforme of iris type recurred in the same location (not in situ) after administration of potassium iodide §
Lipoidine (ethyl ester of diiodized erucic acid) Footnote 10*a*	Recurrent painful folliculitis of left nostril §
Ipecac (emetine) §	
Robert, L.: Un cas d'anaphylaxie locale à l'émétine. Edème envahissant, prurit intense, puis érythème vésiculeux consécutifs à des injections d'émétine, Bull. Soc. path. exot. **15**: 680, 1922.	Local edema appeared at various sites of injections but did not recur in situ

Drugs	Comment
Ipomea (scammony)	
Cerchiai, U.: Un caso di eritema fisso da medicaments (scammonium), Dermosifilographo **6**:542 (Sept.) 1931	In a child aged 7 years a fixed erythema resulted from medication with a mixture containing phenolphthalein, scammony, saccharose and coca. Cerchiai expressed the opinion that the eruption was due to scammony as the other ingredients caused no reactions †
Isacen (diacetyldioxyphenylisatin)	
Ota, M., and Sato, S.: Fixes Laxatolexanthem, die durch Mileval verschlimmerten, Jap. J. Dermat. & Urol. **36**: 83 (Oct.) 1934	Typical erythematous pigmentary patches developed on the neck after the patient took a phenolphthalein preparation; the eruption flared up later after the laxative isacen, not a phenolphthalein preparation, was used
Mercury ‡	
Feldman, A. A., and Serper, W. M.: Ueber fixe Quecksilberexantheme und ihre Verhütung, Russk. vestnik dermat., 1924, no. 1, p. 13; abstr., Zentralbl. f. Haut- u. Geschlechtskr. **16**: 620, 1925	"Fixed" erythema recurred in situ, irrespective of the preparation or of whether it was given intramuscularly or intravenously
Hoffert, E.: Ueber fixes Quecksilber-Exanthem und durch Hautspannung bedingte Quecksilber Ueberempfindlichkeit, Arch. f. Dermat. u. Syph. **147**: 135, 1924	Mild mercurous chloride, mercury bichloride and merbaphen caused a recurrent scarlatiniform fixed patch on the left breast
Hübschmann, K.: Au sujet de la production d'exanthème fixé par l'administration de mercure, Acta dermat.-venereol. **4**: 299, 1923	Fixed erythematous vesicular patches occurred on the flexures of the elbows and knees irrespective of the preparation of mercury used
Langer, E.: Fixe Quecksilberdermatitis, Med. Klin. **18**: 1406, 1922	Bluish red discoloration with itching and burning occurred on the outer aspect of the legs. The first outbreak resulted from mercury subsalicylate, and three relapses occurred after administration of merbaphen.
Phenolphthalein	
Footnotes 6, 13 and 16	Aubrey [10a] and Hunt [10b] reported individual instances of recurrent local pruritus
Wise, F., and Sulzberger, M. B.: Personal communication to the authors	Fixed eczematous patches resulted from an emulsion of phenolphthalein and agar in oil
Quinine ‡	
Abramowitz, E. W.: Erythema Fixé from Quinin, Arch. Dermat. & Syph. **12**: 283 (Aug.) 1925	
Gougerot, H., and Cohen: Quinide érythémateuse fixé par anaphylaxie à la quinine, Rev. prat. d. mal. des pays chauds **7**: 287 (May) 1927	Previous outbreaks resulting from quinine sulfate were followed by a typical fixed erythematous and bullous eruption due to iodoquinate of bismuth
Urbach: Fixes Chininexanthem, Zentralbl. f. Haut- u. Geschlechtskr. **12**: 136, 1924	There was recurrent erythema from quinine sulfate on the left leg, at a site previously affected with a phlegmon
Salicylates ‡	
Acetylsalicylic acid (aspirin)	
Freund, R.: Arzneiexanthem nach Aspirin, München. med. Wchnschr. **52**: 707, 1905	Freund reports a recurrent vesicular eczematous eruption of the hands in two cases and a recurrent herpetic eruption of the prepuce in another, after ingestion of acetylsalicylic acid
Kraus, A.: Ueber Hauterscheinungen bei Aspiringebrauch, Arch. f. Dermat. u. Syph. **119**: 1, 1914	In two patients a recurrent vesicular eruption on the hands with itching and stinging developed after ingestion of aspirin
Sodium salicylate	
Klockov, L.: Ein Fall von fixem Exanthem nach Einnahme von salicylsäuren Natrium, Russk. vestnik dermat. **3**: 47, 1925; abstr., Zentralbl. f. Haut- u. Geschlechtskr. **19**: 246, 1926.	An erythema multiforme type of eruption recurred several times and was located on the neck, nipples, lower lip and glans penis. The same case was reported by Iwanow (Fixiertes Erythema nach Natr. Salicyl. Zentralbl. f. Haut- u. Geschlechtskr. **15**: 37, 1924-1925)

* When no statement to the contrary is made, the cutaneous manifestation was of the erythematous or bullous type, leaving pigmentation.

† There is some doubt as to which drug was the actual cause of the eruption.

‡ The article by Naegeli [10a] gives references not listed here. We have added other and more recent reports.

§ We question whether this eruption is correctly designated as "fixed."

The fixed eruptions have usually followed ingestion of a number of the organic drugs and occasionally have appeared after inorganic substances (bismuth, mercury) had been used. What specific chemical component of these drugs may be the responsible factor remains to be determined. It is possible that any drug on occasions is capable of causing any of the various types of the fixed lesions. A careful search of the literature to date, however, has disclosed that only the drugs listed in the table have caused such eruptions.

Naegeli has observed a fixed herpes of the tongue and has reported the occurrence of fixed papular lesions of the left shoulder after injections of a Bacillus coli vaccine. Naegeli [10a] cited cases in which a fixed urticarial eruption recurred from the drinking of wine and another alcoholic liquor.

"DRUGLESS" FIXED ERUPTIONS

Owing to the fact that in some cases a history of ingestion of drugs cannot be obtained, other sources are believed to be responsible in some cases of fixed eruptions. Wohlstein and Schmidt [21] considered psychic stress and physical exertion the responsible factor in a reported case. Ehrmann [22] connected the eruption with menstruation,[23] and Gougerot [24] attributed it to autotoxic substances (autotoxinides). A spontaneous recurrence soon after the disappearance of a generalized eruption due to phenobarbital was mentioned by Blichert [25] and Jacob [26] and Atzrott [15] reported that a nirvanol (phenylethylhydantoin) rash reappeared without the drug being taken. Naegeli [27] observed a fixed antipyrine eruption that recurred on three different occasions, resulting once from a psychic upset and at another time after inhalation of oil of eucalyptus. Ehrmann [28] reported having observed several spontaneous recurrences of a fixed antipyrine eruption of the genitals (*verge noire* [Fournier]) in a colleague.

21. Wohlstein, E., and Schmidt, L.: Ueber ein fixes Erythem, Dermat. Wchnschr. **89**:1766, 1929.

22. Ehrmann,[2] p. 632.

23. This report antedates the introduction of antipyrine.

24. Gougerot, H.: Dermatoses auto-anaphylactique: Contribution à l'étude des auto-anaphylaxies, J. méd. franç. **19**:160 (May) 1930.

25. Blichert, E.: By-Effects of Luminal, Ugesk. f. læger **75**:1149 (July 3) 1913; abstr., J. A. M. A. **61**:524 (Aug. 16) 1913.

26. Jacob, C.: Ueber Nirvanolvergiftung, Deutsche med. Wchnschr. **45**:1331 (Nov. 27) 1919.

27. Naegeli, cited by Kleeberg, L.: Toxicodermien II, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, p. 350.

28. Ehrmann,[2] p. 657.

Wise and Sulzberger [8d] cited an instance in which a fixed eruption proved to be due to phenolphthalein reappeared after ingestion of a barbiturate [29] and subsequently recurred without further use of any medication.

This brings up certain almost insurmountable difficulties that may arise in the anamnesis in cases in which a drug eruption is suspected. Some foods may be contaminated, medicated with drugs or chemicals [30] or colored with an aniline dye,[31] and the question of other portals of absorption (inhalation, injection, irrigation, instillation, medication by suppositories), exposure to other sources (liquors, cosmetic and toilet preparations), occupation and even surreptitious use of drugs or ordinary forgetfulness must be considered. Because of these possibilities it is difficult to exclude altogether drugs or chemicals as a cause of certain types of dermatoses.

METHOD OF DETERMINING CAUSATIVE AGENT

Careful taking of the history in cases of drug eruptions is highly desirable. Even with the fixed type, the diagnosis is not based merely on the history of certain medication, for other dermatoses may at times easily simulate those produced by drugs. Some persons show or acquire susceptibility to more than one drug. Others may lose their sensitivity to the drug for a time or even permanently. Cutaneous tests are of doubtful value with the fixed type of drug eruption. The presence of the drug in the body fluids indicates only that a certain drug was used. Examination for the drug in the affected skin has so far been reported as successful in only a few cases of fixed bullous lesions from antipyrine.[32] A detailed history, the administration of a small dose of the suspected drug and the subsequent use of several other drugs as controls are the best methods at hand for identifying the suspected agent as a cause of the eruption. If these methods cannot be followed, detailed instructions on avoiding the use of the particular drug may be helpful.

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29. Wise, Fred: Personal communication to the authors.

30. Ownen's Original Laxative Health Bread, report of the Committee on Foods, J. A. M. A. **104**:1708 (May 11) 1935. Abramowitz, E. W.: Phenolphthalein Eruption Produced by the Eating of Iced Cup Cakes, M. J. & Rec. **136**:31 (July 6) 1932. Shelmire, B.: Acne from Iodized Salt, J. A. M. A. **90**: 1869 (June 9) 1928. Cannon, A. B.: Chronic Arsenical Poisoning, New York State J. Med. **36**:219 (Feb. 15) 1936.

31. Baer, H. L.: A Dermatitis Due to Aniline Dye in a Food Product: Report of a Case, J. A. M. A. **103**:10 (July 7) 1934.

32. Tonnel and Raviart: Erythèmes bulleux due à l'ingestion d'antipyrine; leur pathogénie, Echo méd. du Nord **1**:18, 1897. Mibelli.[3]

COMMENT ON THE PATHOGENESIS OF FIXED DRUG ERUPTIONS

Jadassohn[33] early in his investigations on drug eruptions and eczematous dermatitis called attention to the sensitizing properties of drugs and other chemical agents. He observed that the internal or external use of a drug like mercury was capable of causing in some persons an increase in the sensitivity of the skin resulting in a specific type of hypersensitivity and hyposensitivity ("local immunity"). The production of this type of specific hypersensitivity of the skin was closely patterned after that appearing in other specific immunologic processes. Further experimental and clinical studies (Jadassohn, Bloch, Jaeger, Sulzberger and others) revealed that there are certain general and even specific types of cutaneous hypersensitivity that are of a non-immunologic nature, such as the hypersensitiveness of the potentially eczematous persons and the reactions of persons with exceedingly dry skin and those with some inherent biologic abnormality (difference in hydrogen ion concentration, presence of photosensitizing agents or endocrine dysfunction), which explain some of the susceptibilities to certain irritants and possibly to some of the physical agents.

There is a large group of drug eruptions, including the fixed type, that is primarily erythematous, urticarical or eczematous. The idiosyncrasy in such instances is ascribed to the sensitizing property of a drug and not to any poisonous[34] action. Practically any drug is capable of inducing this sensitization. It has been noted that some drugs are more apt to induce sensitization than others and that the frequency with which sensitization may be induced may vary for different lots of the same drug.[35]

ALLERGY

Pirquet's definition of allergy was based on the observations that processes in which preparatory treatment induced immunity to various agents were at times also most intimately connected with apparently contradictory phenomenon, the presence of hypersensitivity. He applied the term "allergy" to the "altered condition which an organism achieves after acquaintance [*Bekanntschaft*] with any organic living or inanimate

33. Jadassohn, Josef: Zur Kenntnis der medicamentösen Dermatosen, Verhandl. d. deutsch. dermat. Gesellsch. **5**:103, 1895; Die Toxikodermien, Deutsche. Klin. **10**:117, 1905; Einige Bemerkungen zum Odolekzem, Zentralbl. f. Haut- u. Geschlechtskr. **7**:158, 1922-1923; Bemerkungen zur Sensibilisierung und Desensibilisierung bei den Ekzemen im Anschluss an einen Fall von Odolekzem, Klin. Wchnschr. **2**:1680 and 1734, 1923; Theoretisches und Praktisches zur Ekzemlehre, Ztschr. f. ärztl. Fortbild. **26**:145, 1929.

34. The word "poisonous" is used in the restricted toxicological sense.

35. Sulzberger, M. B., and Simon, F. A.: Arsphenamine Hypersensitiveness in Guinea Pigs, J. Allergy **6**:39 (Nov.) 1934.

poison," in other words, to the state in which specific hypersensitivity or hyposensitivity and immunity develop.[36]

Allergy apparently covers a wide range of varied manifestations, appearing in both animals and man, which are dependent on a specific alteration of capacity to react (hypersensitivity and hyposensitivity) induced in the organism by sensitization through adequate contact with a definite substance or agent, even a harmless one. Sensitization is indicated in the presence of the following phenomena: a certain period of incubation (exposure to the agent) during which sensitization develops, this period (reaction time) being shortened with subsequent use of the specific agent; the presence of hypersensitivity or hyposensitivity (desensitization); the absence of relationship of the symptoms of reaction to the nature of the agent; capability of the offending agent even in minute amounts of reproducing the reaction, and the specificity for that particular agent or those related (grouped) and occasionally for unrelated substances.

The criteria for allergic hypersensitivity just mentioned, according to Doerr,[37] Bloch,[38] and others, also include the presence of responsible antibodies. According to Pirquet's original definition, the absence of responsible antibodies does not necessarily exclude the phenomena of specific sensitization from being allergic. Specific sensitization in animals and in man is considered a cellular response, and the symptoms are attributed to a union of the circulating allergen with the tissue that has become sensitized.

Protein anaphylaxis is a form of allergy (specific altered reaction) deliberately produced in laboratory animals and characterized by a definite train of symptoms varying with the species employed. The presence of certain specific antibodies (precipitins or allied bodies) is regularly demonstrable. This type of allergy is also believed by some to be encountered occasionally in persons sensitized to foreign serum or other proteins.

One form of human allergy is recognized by Cooke, Coca and others in persons who have been shown to inherit a disposition to a certain type of sensitization. The persons with this disposition have been designated by Coca as "atopic." They have not been proved to show any greater tendency to drug eruptions than those not so constituted, but they are subject to certain forms of asthma, hay fever and atopic

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36. Pirquet, C.: Allergie, München. med. Wchnschr. **2**:1457 (July 24) 1906.

37. Doerr, R.: Allergie und Anaphylaxie, in Kolle, W.; Kraus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed 3, Jena, Gustav Fischer, 1929, vol. 1, p. 973.

38. Bloch, B.: The Rôle of Idiosyncrasy and Allergy in Dermatology, Arch. Dermat. & Syph. **19**:175 (Feb.) 1929.

dermatitis (infantile eczema, neurodermatitis), and occasionally react to certain foods, serums and drugs by showing asthma and hay fever. Antibodies are demonstrable by means of passive transfer experiments (Prausnitz-Küstner reaction). The nature of these antibodies and their causal connection with atopic conditions need further elaboration.

Another form of allergy may appear in man after an adequate exposure to a specific agent, usually without a familial history of atopy and without its antibodies. It is considered the type of allergy encountered in some of the hypersensitivities to foods, serum, bacteria, fungi and drugs and perhaps also in some of the hypersensitivities to physical agents. Cutaneous reactions are a common occurrence in this type, and the mechanism of sensitization is probably analogous to that present in other types of allergy, although responsible antibodies are not regularly demonstrable by present methods. (Antibodies are sometimes demonstrated in some cases of sensitization to food and of serum sickness.)

EXPERIMENTAL AND CLINICAL EVIDENCES OF ALLERGIC NATURE OF HYPERSENSITIVITY TO DRUGS

A drug may be well tolerated for weeks, months or even years until for some reason the person becomes receptive to the sensitizing action of the drug. From observations of those who have been exposed to the drug probably for the first time, the time required for sensitization of the skin to become manifest (appearance of an eruption) is usually from one to two weeks. This period of incubation has striking similarities with that of other specific sensitizations, for instance that exhibited in serum sickness, in nirvanol exanthem and in experimental sensitization to plants and drugs in animals. After cutaneous sensitization is established, the subsequent use of the drug causes the signs of hypersensitivity to reappear much earlier, i. e., within forty-eight hours. Thereafter the cutaneous eruption may be expected to recur with the use of the particular drug (specific reaction) and sometimes with that of chemically related substances (group reaction) or even of unrelated substances (heterophilic reactions?). These cutaneous manifestations usually differ from those produced by the pharmacologic action of the drug, and they can generally be reproduced by doses below the usually effective pharmacologic dose. Similarly, the cutaneous manifestations usually differ from those produced by the poisonous action of the drug. Recurrences are avoided by eliminating the offending drug. Desensitization may develop or at times be produced artificially. As yet no known or regularly demonstrable antibodies have been observed.[39]

39. Sulzberger, M. B., and Wise, F.: Drug Eruptions: II. Dermatitis Eczematosa Due to Drugs, Arch. Dermat. & Syph. **28**:461 (Oct.) 1933.

Schick, Doerr, Landsteiner, Zinsser and other eminent authorities held the opinion that although an antigen-antibody mechanism is far from proved in cases of hypersensitivity to drugs, no other explanation is possible. The experiments with chemically treated proteins by Obermayer and Pick, Landsteiner and Wells support this assumption. Landsteiner's experiments showed that it is possible at times to demonstrate specific antibodies to the chemical component (hapten or partial antigen) of the whole antigen used in producing the sensitization in the experimental animal. The relationship between specificity and the chemical constitution of drugs offers a promising field for the solution of the phenomenon of hypersensitivity to drugs.[40]

The specific hypersensitivity of the epidermis in the eczematous type of drug eruption in man may frequently be demonstrated with the patch test. In cases of the other types of hypersensitivity the scratch and intracutaneous tests are not reliable. The local hypersensitivity of the affected area in a fixed eruption has been demonstrated by means of autotransplant experiments. Whether this local hypersensitivity is present in the epidermal layer or in the underlying structures remains unsettled owing to the varying reports of different observers.[41]

Sensitization has been induced in animals, in man or in both by various substances of a chemical nature. Among the latter may be mentioned the arsphenamines,[42] phenylhydrazine,[43] some of the nitrobenzenes,[44] formaldehyde,[45] primrose,[38] paraphenylenediamine,[46] poison ivy[47] and

40. Landsteiner, K.: The Specificity of Serological Reactions, Springfield, Ill., Charles C. Thomas, Publisher, 1936.

41. Naegeli, O.; de Quervain, F., and Stalder, W.: Nachweis des zellulären Sitzes der Allergie beim fixen Antipyrinexanthem (Autotransplantationen, Versuch in vitro), Klin. Wchnschr. **9**:924 (May 17) 1930. Urbach, E., and Sidaravičius, B.: Zur Kritik der Methoden der passiven Uebertragung der Ueberempfindlichkeit, ibid. **9**:2095 (Nov. 8) 1930. Wise and Sulzberger,[8d] p. 555. Loveman.[7e] Knowles, F. C.; Decker, H. B., and Kandle, R. P.: Phenolphthalein Dermatitis: An Experimental Study Including Reproduction of the Eruption in Skin Transplants, Arch. Dermat. & Syph. **33**:227 (Feb.) 1936.

42. Swift, H. F.: Anaphylaxis to Salvarsan, J. A. M. A. **59**:1236 (Oct. 5) 1912. Frei, W.: Untersuchungen mit Neosalvarsan am Tier, Klin. Wchnschr. **7**:1026, 1928. Sulzberger, M. B.: Hypersensitivity to Arsphenamine in Guinea-Pigs, Arch. Dermat. & Syph. **20**:669 (Nov.) 1929.

43. Jadassohn, W.: Sensibilisierung der Haut des Meerschweinchens auf Phenylhydrazin, Klin. Wchnschr. **9**:551, 1930.

44. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals with Simple Chemical Compounds, J. Exper. Med. **61**:643 (May) 1935.

45. Bernstein, F.: Cutane Sensibilisierung gegen Formalin als berufliche Erkrankung, Dermat. Wchnschr. **95**: 1683, 1932.

46. Mayer, R. L.: Toxicodermien I, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, p. 196.

47. Strauss, H. W.: Artificial Sensitization of Infants to Poison Ivy, J. Allergy **2**:137, 1931. Field, H., and Sulzberger, M. B.: Experiments in Poison Ivy Sensitivity, ibid. **7**:139 (Jan.) 1936.

nirvanol.[48] Silverberg [49] succeeded in sensitizing a number of patients to mesotan (methyloxymethyl ester of salicylic acid) and cited the literature on successful sensitization of the skin to other drugs, like mercury, salicylates, mustard oil, (dihydroxyanthranol) benzene, sodium nirvanol, and the preparations of the orthoform series. Passive transfer reagins have been reported only in isolated and doubtful instances.[50] While it has been possible to produce urticarial and eczematous eruptions with some of the chemical substances, no one has as yet been able to produce a fixed eruption of any type experimentally either in animals or in man. Natural desensitization has sometimes occurred in the case of fixed eruptions, especially after a severe outbreak. Artificial desensitization, sometimes reported in the case of other types of drug eruptions (eruptions from mercury or arsenic), has been successful only in a case of fixed eruption from antipyrine.[51]

Clinically sensitization to drugs may develop either from external or from internal use, and hypersensitivity may subsequently manifest itself with either method of administration. A fixed drug eruption so far as is known appears only as a result of the internal use of the drug and, with the exception of reaction to antipyrine,[4] has recurred only after the internal use of the particular drug.

The term idiosyncrasy is restricted by some investigators to instances in which the hypersensitivity to drugs appears with the first dose of the drug taken. Such instances of specific hypersensitivity are now generally believed to be, although that assumption is difficult to prove, examples of sensitization from an unapparent previous exposure (perhaps in utero) to the same or to an immunologically related substance.

The fact that the hypersensitivity to drugs usually occurs after the medicinal substance has been used for a time has led some observers to explain such reactions by cumulative effects. As some drugs may be retained in the organism for a long period, the reaction that reappears with renewed use of the drug after it has been omitted for many years is also ascribed to cumulation. Meyer and Gottlieb,[52] however, stated that the storing of many powerful drugs in the liver, kidneys, bone marrow or other structures may occur to a considerable degree without

48. Mayer,[46] p. 116.

49. Silverberg, M. G.: Skin Sensitization to Mesotan, Arch. Dermat. & Syph. **21**:166 (Feb.) 1930.

50. Zinsser, H.: Resistance to Infectious Diseases, ed. 4, New York, The Macmillan Company, 1931, p. 370.

51. Widal, F., and Vallery-Radot, P.: Anaphylaxis à l'antipyrine apparue après longue phase de sensibilisation, Presse méd. **28**:93 (Feb. 4) 1920.

52. Meyer, H. H., and Gottlieb, R.: Experimental Pharmacology as a Basis for Therapeutics, English ed. *2*, translated by V. E. Henderson, Philadelphia, J. B. Lippincott Company, 1926, p. 598.

the least injury or change in the function of the respective structures. Even in the case, therefore, of a drug that may have been retained in the body from a prior exposure, cutaneous symptoms appearing from the further exposure to the drug ought to be investigated from an allergic standpoint. A drug eruption is not necessarily due to the drug the presence of which is detected in the organism, nor is it necessarily due to cumulation simply because of the demonstration of a quantitative increase of the drug in the person exhibiting sensitization.

Why the same drug produces one type of eruption in one patient and a different type in another and why several drugs may produce the same type of eruption in some persons is possibly dependent on several other factors, such as the concentration and chemical structure of the drug, the selective action of the drug on the epidermal or underlying tissues, the location of the affected area and also the individual (eczematous) disposition of the patient. This part of the subject requires further study.

The theory that many drug eruptions including the fixed type are of an immunobiologic nature may be accepted on the evidence thus far submitted until definite proof to the contrary is advanced. The mechanism of the reaction as indicated by clinical and experimental studies, although not entirely complete, points to the fulfilment of many postulates for an allergic type of specific hypersensitivity. An antigen (hypothetic)-antibody mechanism is assumed by some to show the close relationship of this type of specific hypersensitivity to another type, i. e., anaphylaxis.

Hypersensitivity to drugs as is well known, develops in certain persons and not in others. The reason for this remains a mystery, although several theories have been advanced as an explanation.

It is due mainly to the work of dermatologists like Josef Jadassohn and Bruno Bloch and their schools and to that of various American and European immunologists that the term idiosyncrasy, formerly used to cloak ignorance regarding the pathogenesis of drug eruptions, now receives a rational explanation. This is not only of theoretical importance but also of practical usefulness. It would be perhaps less confusing if the terminology and definitions at present employed to denote these phenomena received a more generally accepted standardization. Further studies, it is hoped, will lead to this.

SUMMARY AND CONCLUSIONS

The term fixed drug eruption denotes the repeated relapses with a flare-up in situ of the previously affected areas of the skin. It does not refer to the duration of the cutaneous lesions or to the residual pigmentation that may occur as a sequel.

The characteristic (common) fixed drug eruption is the erythematous (or bullous) type. It usually appears on the cutaneous surface but may also affect the orificial mucous membranes.

The less common types of a fixed drug eruption are the urticarial (nodular) and the eczematous, the latter including the erythematous scaly, the follicular, the papular and the vesicular (herpetic or erosive).

Pigmentation usually follows all types of fixed lesions except the urticarial but disappears in time, provided the use of the drug is discontinued.

The fixed drug reactions of exceptional nature are the "lower and outer quadrant" conjunctivitis of Milian; the recurrent "extracutaneous" effects of Jadassohn (peripheral nerve pain in the jaw or in the frontal, or brachial area or submaxillary swelling), and a localized pruritus (or other subjective sensation) recurring in situ.

The following medicinal preparations have been reported as causing various types of fixed drug eruptions: acetophenetidine (phenacetin); acriflavine hydrochloride (trypaflavine); antipyrine, aminopyrine and its compounds; antimony and potassium tartrate; arsenicals (acetylarsan [the para-oxyacetylaminophenylarsinate of diethylamine], arsphenamines, mapharsen, tryparsamide); barbiturates; bismuth salts; cinchophen (atophan); iodides; ipecac (emetine); ipomea (scammony); isacen (diacetyldioxyphenylisatin); mercury; phenolphthalein; quinine and the salicylates (acetylsalicylic acid [aspirin] sodium salicylate).

The characteristic (common) fixed erythematous eruption is generally ascribed to the use of antipyrine and aminopyrine compounds, the arsphenamines, the barbiturates and phenolphthalein, but reports indicate that it may also follow the use of acetylarsan, acriflavine hydrochloride, cinchophen, isacen, mapharsen, mercury, quinine and tryparsamide.

Fixed eruptions are usually due to one drug but on occasions may be caused by another drug used by the patient.

Vaccines and alcoholic liquors are also reported in the literature as a cause for the fixed cutaneous manifestations.

Certain processes such as psychic stress, physical exertion and menstrual disturbances, as well as autotoxic substances, are also stated to have caused fixed types of eruptions.

Proved fixed drug eruptions have been reported to have recurred spontaneously.

The crucial test that a drug is the cause of the fixed eruption is a flare-up in the previously affected area of the skin after the administration of a small test dose of the suspected drug and later of other drugs as controls. Eliminating the use of the suspected drug is another helpful method.

Of the hypotheses submitted as an explanation for the idiosyncrasy to drugs, it may be stated that the present experimental and clinical evidence, while not complete, sustains the concept of an acquired specific hypersensitivity of the skin, localized in the case of the fixed eruptions, due to sensitization of an allergic nature, generally induced by a drug, mostly of organic and occasionally of inorganic composition.

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ABSTRACT OF DISCUSSION

Dr. Marque O. Nelson, Tulsa, Okla.: The idea of a "drugless" fixed eruption is interesting to me. For six years I have had under observation a man with a small round patch of eczema on the back of the hand. During the six year period there have been five or six recurrences at the same time of year, each time in exactly the same area and in a patch of exactly the same shape and size. The eruption clears promptly after treatment with roentgen rays and remains away about a year. There is no history of ingestion of drugs, and I believe that this might be considered an example of a "drugless" fixed eruption. The mechanism by which fixed drug eruptions are produced is not known, but the work of Naegeli, Wise and Sulzberger and Knowles indicates that at least the precipitating cause lies below the skin—probably in the nerves or blood vessels.

Dr. Maurice H. Noun, Des Moines, Iowa: There is one thing which I wish to stress in closing. I believe that many investigators confuse the definition of allergy. According to Pirquet's definition, it is not necessary to be able to demonstrate antibodies in the serum of an allergic person as long as there is a specific altered reactivity in the organism. This altered condition is certainly present in persons who exhibit a fixed drug eruption after the ingestion of a small quantity of the offending drug. Why some people react to drugs and others do not is still unknown. I believe Landsteiner's work with haptens will help considerably in determining this in the near future. At present this subject is still quite complicated and is somewhat of a mystery.

RELATION OF DIET TO CUTANEOUS INFECTION

A STUDY OF THE INFLUENCE OF VARYING CARBOHYDRATE AND FAT INTAKES AND OF FASTING ON EXPERIMENTAL PYOGENIC CUTANEOUS INFECTIONS IN DOGS, WITH COMPARATIVE DETERMINATIONS OF THE GLYCOGEN CONTENT OF THE SKIN AND LIVER

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In view of the frequency with which dietary revision is advised in cases of various pyogenic infections of the skin there exists a rather striking paucity of experimental evidence offering a rational basis for such procedures. Almost all the evidence indicating some association between carbohydrate metabolism and infection is based on observations made on diabetic patients. Many observers, including ourselves, have gained the impression in clinical work that nondiabetic patients with superficial infections of the skin are often found to have been taking excessive amounts of carbohydrates and that in some of these patients adjustment of the diet in this regard is a factor in the production of clinical improvement.

We know of no series of cases in which dietary methods of treatment have been employed exclusively in treating pyodermic infections,[1]

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From the Department of Dermatology and Syphilology, John H. Stokes, M.D., Director, and the Department of Physiological Chemistry, D. Wright Wilson, Ph.D., Director, University of Pennsylvania School of Medicine.

1. Since this paper was submitted for publication, G. M. Crawford and J. H. Swartz (Acne and Carbohydrates, Arch. Dermat. & Syph. **33**:1035 [June] 1936) have reported their experience with ten cases of acne in which the patient was treated for two weeks by daily intravenous injections of dextrose in conjunction with a high carbohydrate intake by mouth. The patient was then discharged from the hospital and advised to continue a high carbohydrate intake and to apply prescribed local medication. After periods of observation varying from six to fourteen months definite improvement was noted in 50 per cent of the cases. Crawford and Swartz presented their findings as a preliminary report. A study of this type is obviously crucial and important, and it is to be hoped that extension of it will allow the obtaining of data on control groups under similar hospital conditions and under dietary treatment alone. The results strongly indicate that the carbohydrate factor is not necessarily a preeminent factor in acne and that improvement may take place regardless of it.

and this lack of adequate controls plus the necessarily somewhat impressionistic character of our clinical observations has served as a stimulus to determine whether or not a result of dietary regulation is demonstrable in animals under controlled conditions. We believe it is probable that a majority of persons with superficial pyodermic infections possess, or at least did possess before the onset of the infection, a normal tolerance for carbohydrates. We were primarily interested, therefore, in determining whether or not diet, particularly the carbohydrate fraction, influences the course of an experimental infection of the skin in normal, nondiabetic animals. To this end we have observed the reaction produced in the skin after intradermal injection of a suspension of living staphylococci and streptococci in fasting dogs and in dogs receiving the following types of diets: "normal" low carbohydrate, high carbohydrate and high fat.

A method of study which allows direct observation of the changes produced in the skin has been selected. It is evident that such a method permits measurement of only gross variation in the response, in contrast to the more exact immunologic methods applicable to studies of the blood. However, it is our opinion that much of the confusion and discordant opinion regarding the relation of cutaneous disease to metabolic changes has been due to comparative ignorance of the physiology and chemistry of the skin itself and to a too persistent attempt to interpret it in terms of the changes in the blood and other organs. The possibilities of the direct observation of the response of the skin to various proteins and bacteria injected intradermally as an experimental procedure have been nicely demonstrated by the work of Kahn,[1a] and he has shown that reactivity of the skin and the serum agglutinin response may vary widely.

The literature relating to the problem of infection and carbohydrate metabolism has been summarized by several writers.[2] One of us, in association with Kulchar,[3] has recently listed the conclusions, some of which are tentative and subject to confirmation of single reports, which may be drawn from such a summary. These are as follows: (1) while diabetic patients show a somewhat increased incidence of cutaneous infections, some patients with severe diabetes may have an entirely

1a. Kahn, Reuben L.: Studies on Tissue Reaction in Immunity: XI. Comparative Response Following Intravenous and Intradermal Injections of Organisms, J. Immunol. **25**:339, 1935.

2. Fischer, J. E.: Blood Sugar Findings in the More Common Diseases of the Skin, Arch. Dermat. & Syph. **26**:970 (Dec.) 1932. Rudy, A.: Urticaria and Insulin Resistance, New England J. Med. **204**:791, 1931. Rost, G. A.: Blutzucker und Haut, Deutsche med. Wchnschr. **55**:173, 1929.

3. Pillsbury, Donald M., and Kulchar, George V.: The Relation of Experimental Skin Infection to Carbohydrate Metabolism, Am. J. M. Sc. **190**:169, 1935.

normal resistance, and the presence of dextrose is not, apparently, the sole reason for the decreased resistance to infection;[4] (2) the blood of diabetic patients is deficient in antibacterial power,[5] but (3) a heightened intake of carbohydrate leads to no marked decrease in antibody formation in the blood of normal dogs,[6] and the simple addition of considerable quantities of dextrose does not lessen its bactericidal power for staphylococci;[7] (4) phlorhizin diabetes heightens the virulence of streptococci but not of staphylococci in rabbits;[8] (5) administration of dextrose in man apparently decreases the self-sterilizing power of the skin,[9] and (6) it is probable that a decreased carbohydrate tolerance is encountered in patients with cutaneous infections and eczema more frequently than in normal persons, but this may be a result of, and not the predisposing factor in, the infection.[10] In a considerable series of patients with furunculosis, Tauber[11] noted a beneficial effect from a high carbohydrate diet, intravenous injections of dextrose and oral administration of liver extract.

Richardson[12] has recently reported a study indicating that in underfed rabbits with a depleted glycogen content of the liver there develops a definitely lower agglutinative titer after administration of typhoid vaccine than in well fed controls with a higher glycogen content of the liver. He found that hyperglycemia maintained by repeated administration of epinephrine has no significant effect on the agglutinative titer developing in rabbits after injections of typhoid vaccine. He pointed out that the state of cellular nutrition is probably more important than the level of the blood sugar in determining antibody response.

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4. Greenwood, A. M., and Rockwood, E. M.: Skin in Diabetic Patients, Arch. Dermat. & Syph. **21**:96 (Jan.) 1930.

5. Richardson, Russell: Immunity in Diabetes: Influence of Diabetes on Development of Antibacterial Properties in Blood, J. Clin. Investigation **12**:1143, 1933.

6. Kleinschmidt, H.: Ernährung und Antikörperbildung, Monatschr. f. Kinderh. **12**:423, 1913.

7. Handmann, E.: Ueber die Ursache der verminderten Resistenz des Diabetikers gegen Infektionen, Deutsches Arch. f. klin. Med. **102**:1, 1911.

8. Franceschelli, D.: Sul rapporte per la presenza di glucosi nell'organismo, Riforma med. **38**:52, 1922.

9. Cornbleet, T.: Self-Sterilizing Powers of the Skin, Arch. Dermat. & Syph. **26**:463 (Sept.) 1932.

10. Ayres, S., Jr.: Glucose Tolerance Reactions in Eczema, Arch. Dermat. & Syph. **11**:623 (May) 1925. Schmidt, E. G.; Eastland, J. S., and Burns, J. H.: Infection and Tolerance for Dextrose, Arch. Int. Med. **54**:466 (Sept.) 1934.

11. Tauber, E. B.: Hyperglycemia in Diseases of the Skin, Arch. Dermat. & Syph. **27**:198 (Feb.) 1933.

12. Richardson, Russell: Immunity in Diabetes: II. Relative Importance of Nutritional State and of Blood Sugar Level in Influencing Development of the Agglutinin After Typhoid Vaccine, J. Clin. Investigation **14**:389, 1935.

In a study of the effect of parenterally administered dextrose on experimental cutaneous infection in rabbits, Pillsbury and Kulchar [3] found that administration of 7.5 Gm. per kilogram daily in two doses had no effect on the course of the experimental infection but that increase of the dose of dextrose to 15 Gm. per kilogram given daily in divided doses at intervals of four hours produced an extensive, rapidly advancing gangrenous infection. However, it was shown that this effect was probably due to some change other than the increased sugar level of the blood and skin as it was found that similar explosive infections followed the injection of large amounts of saline solution of the same tonicity as the solution of dextrose.

EXPERIMENTAL DATA

The animals were placed on the experimental diets for periods varying from seven to ten days, and infection of the skin was then produced by an intradermal injection of broth suspensions of a strain of Staphylococcus aureus-haemolyticus and of two strains of Streptococcus haemolyticus. The course of the cutaneous reaction was then observed, the animal being kept on the experimental diet until healing had occurred. The reaction subsided spontaneously in all but one of the animals, a 2 month old pup on a high fat diet in which death occurred apparently as a result of acidosis and a severe local infection.

Thirty-five adult dogs and three pups were used during the course of these experiments. Twenty-two dogs were subsequently placed on contrasting diets and inoculated again, making a total of sixty experiments. In general the full-grown animals were apparently young. A much more marked susceptibility to infection was noted in the pups, and although we noted no correlation of the age of the dog and the extent of the infection in the obviously young and obviously old adult dogs, the possible influence of such a factor must be kept in mind.

A strain of Staph. aureus-haemolyticus was used for inoculation in all the animals. In twenty-six dogs one of two strains of Strep. haemolyticus was also used. We have observed the course of the infection produced by our strain of Staphylococcus, originally isolated in a case of pyoderma, in over one hundred and twenty-five rabbits, rats [13] and dogs. The strain has had repeated transfers through various animals and has been found to maintain its virulence for three or four months on artificial mediums. Twenty-four hour broth cultures, prepared throughout by the same technician, were found to contain approximately 2,000,000,000 organisms per cubic centimeter.

Care was observed to maintain a uniform technic of intradermal injection of the broth culture. The injection was made as superficially as possible, a fine gage, slightly dull, short needle being used. Duplicate injections on opposite sides of the previously shaved abdominal wall were made in all experiments. The resulting infections showed close uniformity in the same animal. The possibility of varying degrees of infection in pigmented and nonpigmented skin was kept in mind, but no differences were noted. In several experiments duplicate injections with 0.25 and 0.5 cc. of broth culture—four injections in all—were given. In general, the smaller amount produced less evidence of infection, but the differences were not

13. Sternberg, Thomas H., and Pillsbury, Donald M.: The Influence of Avitaminosis A on Experimentally Produced Skin Infections in Rats, Arch. Dermat. & Syph. **35**:247 (Feb.) 1937.

marked. We did not attempt to recover the organisms from the resulting infection in all the animals; however, we have never failed to do so in numerous instances in which the attempt was made. In general, the reaction produced by streptococci was less severe than that produced by staphylococci. Control injections with sterile broth medium and medium containing organisms killed by autoclaving were made. In no instance was any reaction noted.

The reactions to infection were graded on a scale of from 1 to 4. In most instances the reaction was read by both of us independently. In figure 1 are shown the varying sizes of the resulting ulcer on the basis of which the infection was graded. Ordinarily the infection reached its height in about three days and persisted for varying periods proportional to the severity of the reaction. Healing always took place within three weeks of the time of inoculation. The development of an extensive reaction could usually be forecast on the day after the inoculation by the severity of the inflammatory reaction induced.

The experiments were performed on groups of dogs varying in number from five to nine; on the average a group comprised over six dogs. In the smaller groups two contrasting types of diets were given; in the larger groups three types of diet were used. We feel it worthy of emphasis that by this plan we were able to observe the infections in adequate groups under exactly similar conditions of season and temperature, the same organism from the same culture tube being used.

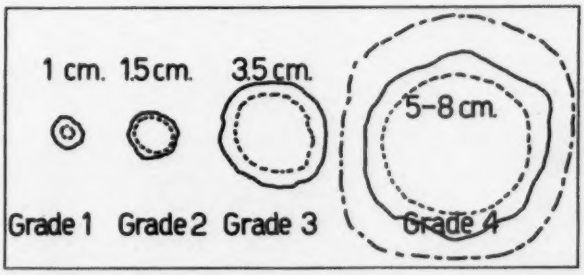

Fig. 1.—Comparative size of ulcers produced in the skin, on which the degree of infection was based. The inner dotted line represents the smallest size in which the reading was made.

The fatty acid-dextrose ratios and the caloric values were calculated from the composition of the ingredients of the diets as given in the tables published by Atwater and Bryant.[14] The foods were obtained from the same sources throughout. The fat content of the ground beef was determined on dried samples by ether extraction in a Soxhlet condenser.[15] It was found to average 25 per cent of the beef, and the fatty acid-dextrose ratios have been calculated on this basis. When suet was used in place of butter, the amount was increased to yield an equivalent amount of fat. The diets were weighed in grams and given in one feeding daily. Sufficient water to make a gruel-like mixture was added. In case of the fasting animals food was withheld for from seven to ten days prior to inoculation. The caloric intake of dogs on a high carbohydrate diet was varied at times to determine the effect of an excessively high caloric supply.

14. Atwater, W. O., and Bryant, M. S.: The Chemical Composition of American Food Materials, Washington, D.C., Government Printing Office, 1906.

15. Blyth, W., and Cox, N. E.: Foods: Their Composition and Analysis, London, Charles Griffin & Co., Ltd., 1927.

OBSERVATIONS

The effects of the diets on the metabolism of the animals have been studied in various ways in representative groups. Data have been obtained on the gain or loss in weight, the sugar content of the blood, the carbon dioxide-combining power of the blood, the water intake and urinary output, the sugar, glycogen and water content of the skin, the glycogen content of the liver and the acetone bodies in the urine.

During the first ten days of the diets the dogs receiving the high carbohydrate diet gained an average of 12 per cent of the original

TABLE 1.—*Types of Diets*

	Gm. per Kg. of Body Weight
Low carbohydrate	
Ground beef	15.0
Powdered skimmed milk	10.0
Suet and butter	1.0
Bone ash	5.0
Salt	0.5
Calories per kilogram, 95 $\frac{FA^*}{D} = \frac{1}{1.3}$	
High carbohydrate	
Ground beef	10.0
Powdered skimmed milk	5.0
Cracker meal	5.0
Sucrose	3.0
Butter and suet	1.0
Bone ash	5.0
Salt	0.5
Calories per kilogram, 100 $\frac{FA^*}{D} = \frac{1}{2.5}$	
High fat	
Ground beef	12
Suet and butter	7
Butter	1
Calories per kilogram, 99 $\frac{FA^*}{D} = \frac{3.8}{1}$	

* $\frac{FA}{D}$ indicates fatty acid-dextrose ratio.

weight; those receiving the high fat diet, an average of 3 per cent, and those receiving the low carbohydrate diet, an average of 0.6 per cent. The fasting dogs lost an average of 12 per cent of the original weight.

Determinations of the sugar content of the blood by the Hagedorn-Jensen method were made on twenty-one dogs, both during fasting and between one and two hours after intake of food. The average level was 84 mg. of sugar per hundred cubic centimeters of blood in animals receiving the high carbohydrate diet, 79 mg. in those receiving the low carbohydrate diet, 72 mg. in those receiving the high fat diet and 70 mg. in the fasting animals. No individual value was outside the normal limits.

Determinations of the sugar content of the skin by the Hagedorn-Jensen [16] method were made on eight dogs two hours after feeding. The values in three dogs on a high carbohydrate diet were respectively 52, 64 and 94 mg. per hundred grams; in four dogs on a high fat intake they were respectively 62, 44, 64, and 99 mg., and in one dog on a low carbohydrate intake the value was 66 mg.

We have naturally been interested in determining whether or not acidosis developed in a group of dogs which received diets high in fat. Table 2 gives the results of tests for urinary acetone and diacetic acid made on fifteen dogs and of determinations of the carbon dioxide-combining power of the blood made on eight dogs.

It is well known that it is more difficult to produce acidosis in dogs by dietary means than in man. In five of seven dogs on a high

TABLE 2.—*Results of Tests for Urinary Acetone, Diacetic Acid and Carbon Dioxide*

Dog	Diet	Tests for Diacetic Acid and Acetone in Urine	Carbon Dioxide Combining Power of Blood
43	High fat	Positive	
44	High fat	Positive	
45	High fat	Positive	
53	High fat	Negative	52
54	High fat	Negative	47
55	High fat	Positive	17
56	High fat	Positive	23
58	High fat	Positive	
46	High carbohydrate	Negative	
48	High carbohydrate	Negative	
50	High carbohydrate	Negative	52
51	High carbohydrate	Negative	52
52	High carbohydrate	Negative	55
47	Low carbohydrate	Negative	
49	Low carbohydrate	Negative	55

fat diet a strongly positive reaction for acetone bodies in the urine was noted; in two of four dogs in which the carbon dioxide-combining power of the blood serum was determined the values were low. Dogs on high and those on low carbohydrate diets showed no evidence of acidosis.

We have obtained determinations of the glycogen content of the liver and skin on fourteen animals on various diets. There are few data available concerning the glycogen content of the skin and, so far as we are aware, its response to changes of diet in normal animals has not been studied. Unna [17] first applied special stains for glycogen to a study of the skin and concluded that the amount present was small.

16. Pillsbury, Donald M., and Kulchar, George V.: The Use of the Hagedorn-Jensen Method in the Determination of Skin Glucose, J. Biol. Chem. **106**:351, 1934.

17. Unna, P. G.: Ueber Verhornung, Med. Klin. **5**:1727, 1909.

Folin, Trimble and Newman [18] stated that the skin contains practically no glycogen. Palmer [19] and Urbach and Sicher [20] mentioned the rapid increase in dextrose content of the skin resulting from postmortem glycogenolysis, and they inferred that considerable amounts of glycogen were present in the skin. Fahrig [21] found values of from 226 to 334 mg. of glycogen per hundred grams in the epidermis and of from 71 to 157 mg. per hundred grams in the corium of human skin. Warren,[22] on the basis of stains for glycogen, has shown that in diabetic subjects the glycogen content of the skin tends to be low. We do not know of any comparative studies of determinations by chemical methods and stains for glycogen.

From the data in table 3 it is immediately apparent that the glycogen content of the skin, in contrast to that of the liver, varies within narrow

TABLE 3.—*Results of Tests for Determination of the Glycogen Content of the Skin and Liver* *

Dog	Type of Diet	Glycogen Content of Skin, per Cent	Glycogen Content of Liver, per Cent
37	Low carbohydrate	0.105	4.09
38	Low carbohydrate	0.110	4.00
39	Low carbohydrate	0.110	4.85
41	High carbohydrate	0.200	11.05
42	High carbohydrate	0.125	16.68
50	High carbohydrate	0.113	12.26
51	High carbohydrate	0.120	8.35
52	High carbohydrate	0.107	11.34
53	High fat	0.068	3.38
54	High fat	0.072	2.81
55	High fat	0.060	0.15
56	High fat	0.083	0.42
58	High fat	0.090	4.08

* The glycogen determinations were made by the method of Good, Kramer and Somogy (The Determination of Glycogen, J. Biol. Chem. **100**: 485, 1933) on tissue obtained from animals under the influence of sodium amytal.

limits at most in response to diet. In the animals receiving a high carbohydrate diet the glycogen content of the liver was from two to four times that observed for the animals receiving a low carbohydrate diet, while the glycogen content of the skin showed only a slight increase,

18. Folin, Otto; Trimble, H. C., and Newman, L. H.: The Distribution and Recovery of Glucose Injected into Animals, J. Biol. Chem. **75**:263, 1927.

19. Palmer, W. W.: The Concentration of Dextrose in the Tissues of Normal and Diabetic Animals, J. Biol. Chem. **30**:79, 1917.

20. Urbach, E., and Sicher, G.: Der Zuckergehalt der Haut unter physiologischen und pathologischen Bedingungen, Wien. klin. Wchnschr. **41**:1481, 1928; Beiträge zu einer physiologischen und pathologischen Chemie der Haut, Arch. f. Dermat. u. Syph. **157**:160, 1929.

21. Fahrig, C.: Ueber den Kohlenhydratumsatz der Geschwülste und ihre normalen Vergleichsgewebe sowie seine Beziehungen zum Milchsäurehaushalt des Körpers, Ztschr. f. Krebsforsch. **25**:146, 1927.

22. Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930, p. 91.

the average value for the dogs on a low carbohydrate diet being 0.107 per cent and in that for the dogs on a high carbohydrate diet 0.129 per cent (107 mg. and 129 mg. per hundred grams, respectively). In animals on a high fat diet the glycogen content of the liver tended to be somewhat lower than in the animals on the low carbohydrate diet; in two cases it was below 1 per cent, while the level for the skin was only moderately lower, averaging 0.07 per cent (70 mg. per hundred grams).

It is not known whether or not the glycogen content of the skin is of importance in the metabolism of this organ. As is the case in many other tissues, there apparently occurs a rapid glycogenolysis with formation of dextrose when skin is removed from the body. It is possible that the glycogen may also be a source for the lactic acid which forms in skin in vitro. However, Pillsbury [23] did not note as rapid accumulation of lactic acid in the skin when glycogen was added as when dextrose was present in the surrounding medium in vitro. He found a more rapid accumulation of lactic acid in well fed rabbits when the skin was removed than was observed in the skin of fasting animals, but this difference was probably due to the increase of available dextrose.

It seems of interest to attempt to determine whether the glycogen in the skin is present as a relatively inert compound, metabolically speaking, or whether it is undergoing more or less constant fluctuation, as is the case with glycogen in muscle or liver. In this connection it should be kept in mind that the skin is a large organ, surpassing the liver in weight,[24] and the demonstration of even moderate metabolic activity in regard to carbohydrate metabolism would be significant.

The metabolism of glycogen in the body occurs in two contrasting ways, one taking place in the liver and the other in muscle. Cori [25] has summarized the differences most clearly. Liver glycogen is the chief source of blood sugar and is constantly undergoing wide variation in response to diet and to the demands of the organism for dextrose. Muscle glycogen, on the other hand, is not available directly as a source of dextrose but forms lactic acid, which in turn may be synthesized into glycogen by the liver. It seems probable that the glycogen content of the skin, in view of the almost negligible variations which are noted after various diets, is not comparable to the glycogen content of the

23. Pillsbury, Donald M.: The Intrinsic Carbohydrate Metabolism of the Skin, J. A. M. A. **96**:426 (Feb. 7) 1931.

24. Vierordt, H.: Anatomische, physiologische und physikalische Daten und Tabellen, Jena, Gustav Fischer, 1906, p. 44.

25. Cori, Carl F.: Mammalian Carbohydrate Metabolism, Physiol. Rev. **11**: 143, 1931.

liver and is probably not a significant source of blood sugar. Additional evidence in this regard is found in the fact that hepatectomized animals do not show a hyperglycemia in response to administration of epinephrine, etherization and asphyxia, indicating that sources of dextrose other than the glycogen in the liver are not available.

As noted, there is little direct evidence to indicate whether or not the glycogen in the skin plays an active rôle in metabolism comparable to that of the glycogen in the muscles. There is some reason for believing that this is not the case. When dextrose is absorbed, approximately 25 per cent of it is taken up by muscle in the form of glycogen.[26] One might, therefore, expect that similar considerable variation of the glycogen content of the skin would occur if the processes were comparable. Furthermore, while it is probable that glycogen disappears from the skin after it is removed from the animal, it seems fairly certain that this disappearance does not occur nearly as rapidly as the disappearance of glycogen from muscle. It is undoubtedly true that in connection with the intrinsic musculature of the skin, the arrectores pilorum, the function of glycogen in the skin is similar to that of glycogen in muscle in general, but there is at present no evidence to indicate that glycogen plays a like rôle in respect to the function of the rest of the skin.

RESULTS OF EXPERIMENTAL INFECTION

The infections noted in relation to the experimental diet on which the animals had been placed are graphically represented in figure 2. Of twenty-two dogs which received a high carbohydrate diet, two had a 4 plus, six a 3 plus, nine a 2 plus and five a 1 plus infection. Of nine dogs kept fasting for ten days before inoculation, one dog had a 4 plus, one a 2 plus and five a 1 plus infection, and two showed no evidence of infection. In eight dogs receiving a high fat intake, one 3 plus infection was noted; the others all exhibited a 1 plus infection. In sixteen animals receiving a low carbohydrate diet, two sustained a 4 plus, two a 2 plus and twelve a 1 plus infection.

It is noted that among the twelve dogs sustaining a severe extensive infection (3 and 4 plus reactions) the incidence according to the type of diet was as follows: one in the fasting dogs; one in the animals on a high fat diet, two in those on a low carbohydrate diet, and eight in those on a high carbohydrate diet.

It is convenient, though perhaps not statistically unimpeachable, to summarize the results in the various groups in terms of average reaction. Such a means of expression does not seem misleading in this

26. Cori, C. F., and Cori, G. T.: VIII. Influence of Insulin on the Utilization of Glucose, Fructose, and Dihydroxyacetone, J. Biol. Chem. **75**:755, 1928.

case. In nine dogs which had been kept fasting the average degree of infection was 1.2 plus; in sixteen dogs on low carbohydrate diets it was 1.5 plus. In eight dogs on a high fat diet the degree of infection was 1.2 plus, and in twenty-two dogs on a high carbohydrate intake it was 2.2 plus.

It has been stated that twenty-two dogs in this series were subsequently infected while receiving diets other than that given at the time of the first inoculation. We wished to follow the course of the infection in the same dog on a contrasting diet. It also seemed of interest to determine if, as might be expected, the animals acquired some degree of resistance to the infection and whether or not this was reflected

FIGURE II

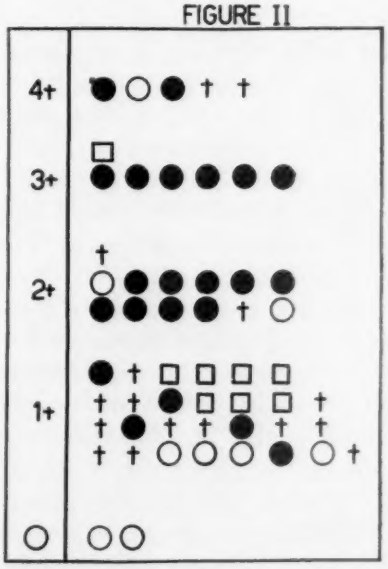

Fig. 2.—Graphic representation of diets in relation to the degree of infection. A low carbohydrate diet is represented by a cross; a high carbohydrate diet, by a black circle; a high fat diet, by a white square, and fasting, by a white circle.

in the cutaneous reactions, thereby giving some indication of the validity of the method as an expression of the immune reaction of the skin. It seemed to us that an increase in the degree of infection in the same animal after the second inoculation might have some significance if it were found to accompany any particular diet with any regularity. It would obviously be inadvisable to include a disproportionate number of dogs on a single diet in either group, and this we have avoided.

In the entire group, irrespective of diet, the average degree of infection observed after the first inoculation was 2 plus; after the second inoculation, 1.45 plus. We interpreted this as an indication of

increased resistance of the group as a whole. In this group, nine dogs were receiving a high carbohydrate diet when they were infected for the first time; among these the average degree of infection was 2.5 plus. Of the remaining thirteen dogs, seven received a low carbohydrate diet and three a high fat diet and three were kept fasting. Considering this group as a whole, the average degree of infection was 1.4 plus. After the second inoculation, twelve dogs on a high fat or a low carbohydrate diet or kept fasting had an average degree of infection of 1 plus (ten had a 1 plus and one, a 2 plus infection, and one had no infection).

COMMENT

We do not know of any adequate explanation for the increased susceptibility of diabetic patients to infection, aside from cases in which a disturbed circulation is demonstrable. It does not seem to us that the mere presence of increased amounts of dextrose, presumably offering a better culture medium for the growth of organisms, has been proved to be a factor. There is some evidence to indicate that a disturbance in water balance may lead to diminished resistance to infection. Clauson [27] has summarized the opinions and evidence concerning this point. He quoted Weigert's [28] studies indicating that the water content of tissues could be decreased by a diet high in fat and low in protein, Berend's [29] cases of pneumonia in children who had previously been fed on diets low in fat and high in carbohydrate, in which a rapid and marked loss of weight was frequently noted at the onset of the infection, and Czerny's [30] theory of exudative diathesis in which some disturbance of the water content of the tissues is an essential feature. He cited Senff's [31] studies indicating that hydrolabile infants have a lowered resistance to infection, particularly to infections of the respiratory tract. Pillsbury and Kulchar [3] cited further evidence on this point, and mention has been made of their work; it indicated that a gross disturbance in the water balance has a profound influence on the course of an experimental infection in rabbits. Kulchar [32] has recently com-

27. Clauson, S. W.: Diet and Infection, Physiol. Rev. **14**:335, 1934.

28. Weigert, R.: Ueber den Einfluss der Ernährung auf die chemische Zusammensetzung des Organismus, Jahrb. f. Kinderh. **61**:178, 1905.

29. Berend, N.: Pneumonie und akute Gewichtsschwankungen bei ernährungsgestörten Säuglingen, Monatschr. f. Kinderh. **9**:241, 1910.

30. Czerny, A.: Die Abhängigkeit der natürlichen Immunität von der Ernährung, Med. Klin. **9**:895, 1913.

31. Senff, A.: Die Bedeutung der konstitutionellen Hydrolabilität für den Verlauf und die Prognose der akuten Infektionskrankheiten dystrophischer Säuglinge, Monatschr. f. Kinderh. **52**:727, 1931.

32. Kulchar, George V., and Alderson, Harry E.: The Relation of the Water-Metabolism to Experimental Skin Infections, Brit. J. Dermat. **48**:477 (Oct.) 1936.

pleted studies the results of which indicated that dehydrated rabbits withstand an experimental infection of the skin as well as, or better than, rabbits on a normal fluid intake and that a quiescent infection may at times be lighted up by the readministration of water.

We are unable to reconcile our results with those of Pillsbury [23] and Kulchar in rabbits, which indicated that dextrose administered parenterally in fairly large amounts (7.5 Gm. per kilogram) had no adverse effect on an experimental cutaneous infection. The possibility of species variation in carbohydrate tolerance must be kept in mind. Intravenous administration of dextrose is, of course, a standard treatment in various infections, and mention has been made of Tauber's [11] results in treatment of furunculosis. It is not clear in Tauber's cases whether his results were due to the high carbohydrate diet, to the intravenous administration of dextrose or of liver extract or, possibly, simply to confinement under the regular regimen of hospital life. A possibly analogous paradox is seen in the extended studies of Craven [33] on arsphenamine intoxication, in which he found that a high intake of carbohydrates by mouth predisposed dogs to hepatic damage from arsphenamine. Clinically the intravenous administration of dextrose in arsphenamine dermatitis and hepatitis has been shown to be beneficial (Shaffer [34]), and Stokes [35] has suggested that Craven's results may have been due to the effect of a high carbohydrate diet on the production of toxin by micro-organisms in the intestinal tract rather than to a specific effect of the carbohydrate. In this connection we have noted a marked tendency to diarrhea and foul stools in our dogs on a high carbohydrate intake; this was, however, controlled in part by the administration of bone ash.

One of us [23] has summarized the evidence indicating that changes in the lactic acid content of the skin may well have an effect in increasing the growth of organisms and in producing functional changes in the vascular structures of the skin.

SUMMARY

In groups of dogs receiving low carbohydrate, high carbohydrate and high fat diets and in a group of fasting dogs the reaction to the intradermal injection of broth suspensions of living staphylococci and streptococci has been followed. The cutaneous infections were in general

33. Craven, E. B.: The Importance of Diet in Preventing Acute Yellow Atrophy During Arsphenamine Treatment, Bull. Johns Hopkins Hosp. **48**:131, 1931.

34. Shaffer, L. W.: Treatment of Postarsphenamine Dermatitis, Arch. Dermat. & Syph. **29**:173 (Feb.) 1934.

35. Stokes, John H.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1934, p. 452.

definitely more severe in animals on a high carbohydrate intake than in those on a low carbohydrate or a high fat diet and in fasting dogs.

Representative determinations of the sugar content of the blood indicated that no significant variations from normal occurred. In six of eight animals given a high fat diet evidence of acidosis developed; the infections noted in these animals with one exception were mild.

The glycogen content of the skin showed but slight response to variations in the diet, and there was no evidence indicating that it was of any great importance in the metabolism of the skin or in the organism as a whole.

CONCLUSION

The course of an experimental infection of the skin is more severe in animals on a high carbohydrate intake than in animals on a low carbohydrate or a high fat intake or in fasting animals.

Dr. H. M. Vars of the Department of Research Surgery, University of Pennsylvania School of Medicine, made the glycogen determinations and Dr. Samuel Goldschmidt of the Department of Physiology gave suggestions regarding the high carbohydrate diets.

ABSTRACT OF DISCUSSION

Dr. John F. Madden, St. Paul: Dermatologists are constantly facing the problem of evaluating diets, and most of them have little accurate experimental evidence on which to base their decisions. I am sure that all welcome this work, which is a step toward putting dietetic treatment in dermatology on a scientific basis. One should not only continue to substitute dietary facts for vague impressions but also strive to arrive at uniformity in dietetic treatment which is almost entirely lacking among dermatologists.

Dr. Pillsbury and Dr. Sternberg have shown that the course of experimental infection of the skin is more severe in animals on a high carbohydrate diet than in animals on other diets. There must be a great difference between a normal person on a high carbohydrate diet and a diabetic patient. It is true that diabetic persons who are sugar free are less susceptible to infection than those who are not sugar free, but in my experience persons with even the most carefully controlled diabetes who have a normal amount of sugar in the blood are much more susceptible to infection than normal persons. This is particularly true when minor infections, such as the balanitides, are considered. The underlying chronic diabetes itself must lower the patient's resistance and make him more susceptible to infection, regardless of the sugar content of the blood.

Dr. Arthur Schoch, Dallas, Texas: The interesting feature in the experiments reported is that there was apparently no appreciable increase in the glycogen content of the skin to explain the phenomenon on an alimentary basis.

I wish to ask Dr. Sternberg and Dr. Pillsbury what hypothesis they have to offer for the increased susceptibility of the skin to staphylococci in the presence of these altered diets.

Dr. Theodore Cornbleet, Chicago: In my work on the self-sterilization of the skin among other phases that I considered was that of carbohydrate metabolism. I found that in man the ingestion of a certain amount of sugar impaired the skin's ability to sterilize itself, and the impairment was manifest, whether the tests were

made for staphylococci or for streptococci. When a person ingests a certain amount of sugar, the sugar content of the blood goes through a certain cycle. That cycle may be depicted by a graph known as a dextrose tolerance curve. From the base, or fasting, level there is a rather abrupt rise in the value for sugar, which levels off and then tapers down again toward the fasting level a little bit more slowly than it rose. When it reaches the fasting level it does not stay there. From there on begins the negative phase of the curve, which dips below the fasting level.

I found that the impairment of the skin's power of self-sterilization occurred particularly during that negative phase and that this impairment was particularly marked if the person's curve for sucrose tolerance was abrupt and the phases were deep.

I do not know how to explain this phenomenon. One feature, however, suggests itself, namely, that the decrease in sugar content of the blood is accounted for by the sucking of sugar from the blood into the muscles and the skin. In that case the skin would be flooded with sugar to be potentially made into glycogen.

It is known that workers in sugar refineries are susceptible to infection, and it may be that the rapid increase in the sugar content of the skin has the same action as the surface sugar has on the workers in sugar refineries.

I wish to refer to the findings of Dr. Pillsbury and Dr. Sternberg in the dogs on high fat diets. I have often been puzzled by the fact that in irritated skin, in skin with a dermatitis and in skin with a broken surface infection develops so infrequently. In my recent work I have found that in an area affected with a dermatitis ketone bodies develop; that is, the carbohydrate metabolism of such an area is impaired. The equivalent state exists in diabetic patients in whom sugar cannot be metabolized to its final materials, namely, carbon dioxide and water, but in whom ketone bodies, that is to say diacetic acid and beta-oxybutyric acid, form. It may be that these ketones protect the skin from infection, just as they may eradicate infection from the genito-urinary tract, a ketogenic diet being given in order to produce these ketone bodies.

Dr. Victor E. Levine, Omaha: There are many researches on the relation of diet to systemic infection, but there are few on diet in relation to local infection. The paper of Dr. Pillsbury and Dr. Sternberg is therefore timely.

I wish to discuss their paper with particular reference to the diet of their dogs and to the conclusions they have drawn from their work. It must be recognized that in an experimental work involving nutrition there are many pitfalls. The dogs to be used must be healthy. They must be made to subsist on an adequate diet before they are placed on any experimental diet. If the dogs are not in the best physical condition, are not free from infection and are not on a well balanced diet before the experimental ration is begun, any nutritional result may be obtained.

According to the authors, some of the dogs were kept fasting, and some received a high carbohydrate diet, some a low carbohydrate diet, some a low fat diet and some a high fat diet. It seems to me that no precaution was taken to insure balance and adequacy in the diets with changing amounts of carbohydrate or fat.

In going over the data on the dietary ingredients used, it seems that there is a shortage on the side of water-soluble vitamins and fat-soluble vitamins. Calcium occurs in plentiful amount because of the inclusion of calcium salts which set off the low intake of calcium occasioned by the use of meat.

That the high fat diet did not produce as much infection as the low fat diet may be due to the greater intake of butter and therefore to the greater intake of vitamin A, which renders the skin less susceptible or more resistant to infection. On the other hand, it must be conceded that if a diet is high in carbohydrates, it must be low in some other dietary constituents. The sins of nutrition are not sins

of commission but sins of omission. It is likely that in the experimental diet rich in carbohydrate something has been omitted which is essential to the nutrition of the skin.

It is a well known fact that by subjecting an animal to starvation one cannot produce any typical vitamin deficiency. It is only on an unbalanced ration that vitamin deficiency reveals its special pathologic features.

It would be dangerous to say that prescribing a high carbohydrate diet is the way to treat and prevent cutaneous infection. One must analyze the diet with respect to each essential nutritional factor lest one give the wrong label to a situation and thus hide the real truth.

DR. MOSES SCHOLTZ, Los Angeles: There is another angle of dietetic control in local infection, namely, the element of biologic resistance of the system to the infection. It is an old clinical observation that there are many kinds of chronic pyogenic infection which refuse to yield because of the low systemic resistance. I remember a series of patients presented at the Mayo Clinic a few years ago, patients with severe streptococcic lesions which refused to heal until the patients were put on a high vitamin diet. This fact is also confirmed theoretically. It was demonstrated long ago that vitamin A contributes to protection of the integrity of the epidermis. A dry, cracked skin is a portal for infection, and for that reason one must differentiate between acute pyogenic infection in persons with high sugar content of the blood taking food with a high carbohydrate content and chronic pyogenic infection. One is apt to overlook this factor of a low nutritional condition and vitamin deficiency. For this reason, in chronic pyogenic infection, besides reduction of the sugars and starches one should not fail to prescribe a high vitamin nutritional diet.

DR. DONALD M. PILLSBURY, Philadelphia: With regard to Dr. Schoch's question as to the theory of the mechanism which is concerned in our results, we have no adequate theory, but there are several possibilities considered in the complete paper.

I was interested in the remarks Dr. Cornbleet made regarding the presence of ketone bodies in animals on a high fat diet. I wish to point out, however, that it has been assumed that the action of a high fat diet in pyuria is due to the change in p_H of the urine. I think that that is probably correct. It must not be forgotten, however, that possibly these ketone bodies or some change in acidity of the skin induced in connection with the high fat diet may be a factor in protecting the skin from infection.

It must also be pointed out that diabetic patients with acidosis have long been assumed to be particularly vulnerable to infection.

I do not have any particular remarks to make in connection with the curve for dextrose tolerance to which Dr. Cornbleet has referred. I differ with him somewhat about the phrase that the skin "sucks out" sugar from the blood. It is known from the work of Folin, Trimble and Newman and from that of Urbach that when there is an increase in the sugar content of the blood the sugar content of the skin rapidly rises. It has been shown, however, that this is a temporary change; the skin is not a permanent reservoir for dextrose, and there is no evidence to indicate, at present at least, that transformation of dextrose into glycogen occurs in the skin.

Dr. Levine has raised a number of important points which must be considered in the interpretation of a study of this sort. I should like first to assure him that we are not presumptuous enough to conclude on the basis of these studies that every patient with a cutaneous infection should be treated by means of a low carbohydrate diet. I have seen patients in whom serious effects on the general

health had been produced by a too strenuous application of this hypothesis. The need for experimental study seems obvious, and the present work is presented as one phase thereof. In what measure a study on dog skin can be applied to human beings one cannot say; this is one of the constant difficulties of experimental dermatology. At least one can control the conditions of the experiment adequately, and this is often impossible in ambulatory patients.

The dogs used in these experiments were carefully selected on the basis of good general condition and young adult age. They had previously been on adequate diets. We have considered the question of the influence of variation in the vitamin intake. There is definite reason to believe that in the relatively short time involved in these experiments, especially in adult dogs, significant decreases in the vitamin stores could hardly occur. Furthermore, such vitamin deficiencies as did exist were present throughout all the diets. All the animals received adequate amounts of butter, and the excess fat in the high fat diets was obtained by increasing the intake of suet.

Furthermore, I should like to ask what experimental evidence Dr. Levine can offer for his statement as to the definite influence of vitamin A on infection of the skin. In a recent study Sternberg and I were impressed by the paucity of data on this point. In a series of rats with extreme symptoms of avitaminosis A we found no indication of any decrease in the resistance of the skin to infection with staphylococci. The cutaneous infections healed promptly while the animals were dying of vitamin A deficiency.

I should also like to point out that in twenty-two instances the same animal was subsequently reinfected while a contrasting diet was being given. We have been careful to be certain that significant variations in vitamin content of the contrasting diets were not present. It seems to me that such variations as were observed in the infections obtained must be attributed in large measure to the differences in the carbohydrate and fat fractions of the diet as such.

In regard to a clinical condition such as acne there has always been a question in my mind as to how much of the dermatosis may be attributed to lack of resistance to infection and how much is due to allergy or some unknown factor. It is in some respects remarkable how much resistance patients with acne actually display when one considers that they are constantly carrying innumerable foci of infection in their sebaceous glands, that they ordinarily enjoy good average general health and that they almost never fall prey to serious dissemination of their infection. There are many factors in the problem; we realize that the carbohydrate metabolism is only one, and we are attempting to determine whether it is of great or of small importance.

STERNAL PUNCTURE

A DIAGNOSTIC AID IN LEUKAEMIA CUTIS; A POSSIBLE AID IN DIFFERENTIATING THE LYMPHOBLASTOMAS

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AND

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Much has been written during the past years concerning the so-called lymphoblastomas. Opinions as to the proper classification of this group of diseases have varied widely. Theories have included a neoplastic and an infectious background. Some observers have referred to the members of this group as separate clinical entities; others have preferred the explanation of genetically related variations of a common tissue source. More recently there seems to be an increasing agreement of opinion among those interesting themselves in this particular group of diseases. Keim's [1] statement suggesting a common origin in the hematopoietic or reticulo-endothelial system is apparently accepted by an increasing number of investigators. According to a recent statement by Wile,[2] the occurrence of mutations as well as their significance ". . . constitutes strong evidence in favor of the view that lymphoblastomas are genetically related neoplasms involving the lymphoid tissues." It was this growing conception of a constant or frequent relationship to the blood-forming organs that suggested to us the investigations reported herein.

Simultaneous studies of the bone marrow and the circulating blood in living subjects may be said to be a relatively recently developed diagnostic procedure. In this country the more recent studies include those reported by Young and Osgood,[3] Reich [4] and Dameshek.[5] As a

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1. Keim, H. L.: The Lymphoblastomas, Arch. Dermat. & Syph. **19**:533 (April) 1929.

2. Wile, Udo J., and Stiles, Frank, Jr.: Clinical Mutations in Lymphoblastomas, J. A. M. A. **104**:7 (Feb. 16) 1935.

3. Young, R. A., and Osgood, Edwin E.: Sternal Marrow Aspirated During Life, Arch. Int. Med. **55**:186 (Feb.) 1935.

result of these and related investigations it has become increasingly apparent that the circulating blood not infrequently fails to furnish accurate information concerning underlying abnormalities in the blood-forming organs. Ordinarily the lymphoid tissue, the reticulo-endothelial system and the bone marrow are regarded as the source of the cells in the blood stream. Their rate of release, the phenomena of growth and destruction, the fundamental processes influencing numbers and morphology—each an important factor—may well be evidenced earlier at their source than elsewhere. Furthermore, from the aforementioned studies there seems to be abundant evidence to show that while different pathologic states may present somewhat similar changes in the peripheral blood, distinguishing characteristics of these states may often be observed in the bone marrow. While the diagnosis of diseases of the blood-forming organs may usually be deduced from clinical and laboratory evidence, occasionally a case occurs in which, at a given time, it is impossible to arrive at a diagnosis in that way. It is in such cases, as shown definitely in the investigations referred to, that the value of study of the bone marrow has been convincingly demonstrated. As we had in mind the information obtainable in this manner, the application of this procedure in a study of the various subdivisions of leukemic involvement of the skin and allied conditions seemed worthy of trial.

The technic of sternal puncture which we have employed has been described in detail elsewhere.[3] Briefly, it is as follows:

With the patient lying on the back with a pillow under the shoulders, the area of the sternomanubrial joint is prepared with iodine and alcohol. Under aseptic technic the skin, the subcutaneous tissues and the periosteum over the sternomanubrial joint are anesthetized with 1 per cent procaine hydrochloride, and four minutes is allowed to elapse for the anesthetic to take effect. A 16 gage spinal needle, cut off to 3.5 cc. and rebeveled, is introduced vertically into the sternomanubrial joint. The needle is then inclined to an angle of about 30 degrees with the plane of the sternum, and, being rotated, is inserted into the marrow cavity of the sternum. The stilet is removed and from 1 to 2 cc. of marrow aspirated into a tight 10 cc. syringe. This is introduced into a tube containing 2 mg. of oxalate for each 2 cc. of marrow and shaken vigorously. On this marrow, which looks like blood, any of the methods used for oxalated blood[5b] may be used. As a routine a red cell count, a nucleated cell count and a differential count of 500 cells are made,

4. Reich, Carl: A Study of the Diagnostic Value of Sternal Puncture in Clinical Hematology, Am. J. M. Sc. **189**:515 (April) 1935.

5. (*a*) Dameshek, W.: Biopsy of the Sternal Bone Marrow, Am. J. M. Sc. **190**:617 (Nov.) 1935. (*b*) Osgood, E. E.: A Textbook of Laboratory Diagnosis, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1935, p. 585. (*c*) Osgood, E. E.; Haskins, H. D., and Trotman, F. E.: A Uniform System of Hematologic Methods for Use with Oxalated Venous Blood, J. Lab. & Clin. Med. **16**:476 (Feb.) 1931. (*d*) Osgood, E. E., and Ashworth, Clarice A.: An Atlas of Hematology, San Francisco, J. W. Stacey, Inc., 1937.

and peroxidase stains and reticulocyte counts are made when indicated. Full details of the technic and interpretation are given in the references.[6]

For the purposes of this paper a sternal puncture has been considered to indicate the presence of myelogenous leukemia if the premyelocyte count exceeded 20 per cent or the myeloblast count exceeded 4 per cent and to be suggestive of myelogenous leukemia if the premyelocyte count was between 10 and 20 per cent or the myeloblast count was between 2 and 4 per cent. Lymphatic leukemia was considered to be indicated if the lymphocyte count exceeded 20 per cent or if more than from 5 to 20 per cent of lymphocytes or any large lymphocytes were present. Lower values than those mentioned were considered to indicate absence of either myelogenous or lymphatic leukemia. In normal marrow the total number of nucleated cells is usually under 70,000 per cubic millimeter.

The studies have been made on both ambulatory and hospitalized patients observed in dispensary and private practice. So far as possible a detailed study has been made in each case. This has included repeated blood counts, repeated sternal punctures, biopsies, and, in cases in which death occurred, autopsy. The patients who were still living when the survey was made have been recalled for occasional observation when possible. Periods of observation have varied from a few days to nearly three years. Clinical photographs and photomicrographs, as well as detailed case histories, have not seemed an essential part of this report. The cases studied have been grouped to emphasize certain clinical features and associated laboratory observations. The results are as recorded in tables 1, 2, 3 and 4.

COMMENT

Table 1.—Cases 1, 2, 3 and 4 have been chosen from a larger series of cases of similar conditions reported elsewhere. They are presented as typical examples of fairly common clinical pictures. As indicated, the results of the usual examination of the blood were decisive in case 1, doubtful in case 2 and entirely negative in cases 3 and 4. In this same group the sternal marrow gave uniform information of diagnostic value as proved by subsequent events in each case. Presumably the presence or absence of cutaneous involvement would have been without influence on these observations. It was experiences of this type which prompted our original decision to include only the varieties of leukemia in this report. Further consideration of conditions illustrated by cases 5 and 6, in which the clinical changes on the skin when present may lead to confusion, resulted in the inclusion of a larger group of cases. Consequently it was decided to include in the study an appraisal of the diagnostic value of sternal puncture in cases of leukemia as well as an appraisal of the procedure as a differential aid in instances of certain

6. Young and Osgood.[3] Footnote 5.

TABLE 1.—*Observations on Patients Without Cutaneous Involvement*

Case Number	Patient	Age	Sex	Complaint on Entrance	Blood Picture	Sternal Marrow Picture	Clinical Findings	Results of Biopsy	Additional Data and Final Diagnosis
1	H. C.	63	M	Coma	Acute myelogenous leukemia	Acute myelogenous leukemia	General adenopathy	.....	Necropsy; acute myelogenous leukemia
2	L. P.	66	M	Weakness; pain in joints	Suggestive	Chronic lymphatic leukemia	General adenopathy; general weakness	.....	Subsequent observation (blood) substantiating diagnosis of chronic lymphatic leukemia
3	E. S.	64	M	Weakness; shortness of breath	No leukemic changes	Chronic aleukemic myelogenous leukemia	General pallor; weakness; loss of weight	.....	Necropsy; chronic aleukemic myelogenous leukemia
4	L. C.	19	F	Fever; pain in joints	No leukemic changes	Acute aleukemic lymphatic leukemia	General adenopathy; enlarged spleen	.....	Necropsy; acute aleukemic lymphatic leukemia
5	A. B.	28	M	Swelling in right cervical region	No leukemic changes	No leukemic changes	General adenopathy; enlarged spleen	Involvement of cervical lymph nodes; Hodgkin's disease	Patient under observation; clinically progressive Hodgkin's disease
6	J. K.	38	M	Cervical adenitis	No leukemic changes	No leukemic changes	Enlarged cervical, axillary, epitrochlear and inguinal glands	Lymph glands showing marked hyperplasia suggestive of malignant disease	Patient under observation; final clinical diagnosis, lymphosarcoma

TABLE 2.—*Observations on Patients with Cutaneous Involvement and Leukemic Changes in the Blood and Sternal Marrow*

Case Number	Patient	Age	Sex	Complaint on Entrance; Duration	Blood Picture	Sternal Marrow Picture	Clinical Findings	Results of Biopsy	Additional Data and Final Diagnosis
7	H. O.	21	M	Weakness; fever; rash for 4 weeks	Acute myelogenous leukemia	Acute myelogenous leukemia	Papular infiltrations on extremities	.....	Patient died 2 days after entering hospital; necropsy; acute myelogenous leukemia
8	G. V.	64	M	Nodular growths on face for several weeks	Chronic lymphatic leukemia	Chronic lymphatic leukemia	Typical nodules on the face, ears and neck	Lymphosarcoma	Examination of blood and sternal marrow and clinical observation since Nov. 1934 all pointing to diagnosis of chronic lymphatic leukemia rather than lymphosarcoma
9	E. L.	48	M	Cutaneous eruption for two months	Chronic lymphatic leukemia	Chronic lymphatic leukemia	Scaling erythroderma	Leukaemia cutis	Disappeared from observation; somewhat improved by symptomatic treatment
10	F. H.	58	M	Cutaneous eruption for several months	Chronic lymphatic leukemia	Chronic lymphatic leukemia	Scaling erythroderma	Leukaemia cutis	Chronic lymphatic leukemia; necropsy

allied pictures. It is interesting to note here that Dameshek, using a somewhat different technic, has in certain cases been able to make ante mortem a diagnosis of Hodgkin's disease and lymphosarcoma which was confirmed only after necropsy.

Table 2.—Herein are included cases of various types of cutaneous involvement. In this group the circulating blood and the sternal marrow have given uniformly identical diagnostic evidence. In these cases, therefore, sternal puncture has furnished merely additional or confirmatory diagnostic information. The evident fact remains, however, that in the cases included in tables 1 and 2 the accuracy of information furnished by the observations on the bone marrow is greater than that obtained by study of the blood. It is further noteworthy in case 8 that the histologic picture was a confusing factor. The varying histologic picture at times caused by the diseases under consideration is well known. This fact, it seems, makes more valuable every possible additional diagnostic aid in investigative studies of these conditions.

Table 3.—Observations on cases 11 and 12 are presented together because in each the blood picture gave no diagnostic assistance, yet the clinical findings seemed to favor the diagnosis of a leukemic process. Furthermore, in case 11 it was impossible for the pathologist to furnish decisive evidence. It is worthy of note that a diagnosis made possible by sternal puncture was confirmed at necropsy. In case 12 the blood picture likewise was normal, yet the observations on the bone marrow have agreed with the histologic evidence, the roentgenologic evidence of changes in the bones and repeated subsequent observations.

Table 4.—The three cases summarized in this table are presented as suggestive of the possible value of the procedure in differential diagnosis. In case 13 the patient entered the hospital on account of a rather large, irregularly shaped ulcer involving the perineal region. In addition to this, examination revealed painless noninflammatory nodular and plaquelike infiltrations of the abdomen. A tentative clinical diagnosis of leukaemia cutis was made in spite of negative results of examination of the blood and material obtained by sternal puncture. At first the clinical diagnosis of aleukemic leukemia was sustained by the results of histologic examination. Further study and prolonged observation showed complete clinical recovery and apparently substantiated a final diagnosis of relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian's disease). The value of the negative results of examination of the bone marrow is suggested by the sequence of events in this case.

In case 14 the patient has been under observation on repeated occasions. We have witnessed several remissions and recurrences of a scaling erythroderma with an accompanying general lymphadenitis and

TABLE 3.—*Observations on Patients with Cutaneous Involvement, No Leukemic Changes in the Blood and Diagnostic Changes in the Sternal Marrow*

Case Number	Patient	Age	Sex	Complaint on Entrance; Duration	Blood Picture	Sternal Marrow Picture	Clinical Findings	Results of Biopsy	Additional Data and Final Diagnosis
11	L. C.	19	F	General pruritus for 2 or 3 months	No leukemic changes	Aleukemic leukemia	Mild general erythroderma; some thickening and adenitis	Lymphoblastoma, type not determined	Necropsy; chronic aleukemic leukemia
12*	M. B.	50	M	Loss of weight for several months	No leukemic changes	Myelogenous leukemia	Nodular infiltration on abdomen and chest	Leukaemia cutis	Final diagnosis, aleukemic myelosis with involvement of skin, bones and other organs

* Drs. Laurence Selling and Thomas Robertson, Portland, Ore., gave permission to include this case.

TABLE 4.—*Observations on Patients with Cutaneous Involvement and no Leukemic Changes in the Blood and Sternal Marrow*

Case Number	Patient	Age	Sex	Complaint on Entrance; Duration	Blood Picture	Sternal Marrow Picture	Clinical Findings	Results of Biopsy	Additional Data and Final Diagnosis
13	E. O.	17	F	Perineal ulceration for several months	No leukemic changes	No leukemic changes	Pyogenic ulcer of perineum, nodular infiltration on abdomen suggesting leukemia cutis	(1) Myelogenous leukemia of skin and subcutaneous fat; (2) relapsing febrile nodular panniculitis	Complete recovery; diagnosis: relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease)
14	J. P.	67	M	General scaly eruption, pruritis for 3 years	No leukemic changes	No leukemic changes	Scaling erythroderma	1932, leukaemia cutis; 1936, lymphoblastoma (?) suggestive of mycosis fungoides	Recent observation revealing areas of infiltrated pruritic eczematoid dermatitis suggestive of mycosis fungoides
15	G. D.	53	M	Weakness for several months	No leukemic changes	No leukemic changes	Exfoliative dermatitis, lymphadenitis	Hodgkin's disease; Dorothy Reed cells	Patient under observation

pruritus. Until recently, notwithstanding consistently negative result of examination of both the blood and the sternal marrow, the diagnosis has been that of a diffuse (aleukemic) leukaemia cutis. In 1932 this original diagnosis was confirmed by biopsy. When the patient was recalled for observation recently a changed clinical picture was found. Scattered, moderately infiltrated eczematoid areas had replaced the uniform generalized involvement observed previously. These, together with the symptoms of pruritus, now suggested a developing mycosis fungoides. The pathologic report at this time was "lymphoblastoma, possibly mycosis fungoides."

Finally, the observations in case 15 are presented because of the clinical findings of a general exfoliative process associated with a general lymphadenopathy—a picture of lymphoblastoma. Again the blood and material obtained by sternal puncture were normal; this furnished negative evidence which was sustained by the results of biopsy, Dorothy Reed cells and a continued progression of typical Hodgkin's symptoms being observed.

SUMMARY

The number of cases reported here is small. The evidence obtained, therefore, is presumptive rather than conclusive. Continued use of the method may reveal that occasionally it is inadequate; however, so far as these fifteen cases are concerned, sternal puncture has furnished information of noteworthy diagnostic accuracy. This has applied to diseases with and without cutaneous involvement and has included most members of the so-called lymphoblastoma group. In the cases studied it gave information of greater accuracy than was obtained either by examination of the blood or by biopsy. What might be termed the "positive" value of the procedure has been limited to the various subdivisions of leukemia. Its "negative" value has been indicated in cases of Hodgkin's disease and of lymphosarcoma and in a case presumed to be one of mycosis fungoides. Its "positive" value has included two of the latter three conditions in the experience of Dameshek. The technic used is simple, applicable to ambulatory patients and free from disagreeable symptoms or sequelae. It is true that proper interpretation of observations demands the judgment of one trained in this particular type of work. Finally, it would seem fair to assume, as was recently suggested by Weidman and Custer,[7] that any diagnostic or investigative procedure about which these statements may be made well merits further trial in future studies of this group of diseases.

7. Weidman, Fred D., and Custer, R. P.: The Scope of the So-Called "Cutaneous Lymphoblastomas" in Relation to Lesions of the Hematopoietic System, in Deliberationes Congressus Dermatologorum Internationalis IX-i, Budapest, L. Nekam, 1936.

CONCLUSIONS

A simple method of sternal puncture is reviewed.

Observations on the bone marrow in cases of leukemia cutis, of Hodgkin's disease and of lymphosarcoma and in one case of what was possibly mycosis fungoides are reported.

Information obtained in this manner seems to justify further use of this method in diagnostic studies of these diseases.

ABSTRACT OF DISCUSSION

DR. HARTHER L. KEIM, Detroit: Dr. Kingery has called attention to a diagnostic aid which is relatively simple but which it seems to me will help to throw considerable light over a period of years on the proper interpretation of the diseases called lymphoblastomas. In spite of the newness of this diagnostic procedure it is rapidly taking its place among the other laboratory aids utilized in this group of diseases. All dermatologists have had under observation for varying periods cases of diseases considered to be clinical examples of lymphoblastoma. However, no known laboratory methods then available gave the help necessary to establish the diagnosis definitely. It seems to me that with the help of the procedure described by the authors it will be possible during the life of the patient to get information from the blood and bone marrow which previously has not been obtainable. Not only can this information be obtained earlier but, as the authors said, it will be much more accurate, and as time goes on and more sternal punctures are made it will be possible to demonstrate the hematologic interrelationships in this group of diseases. Certainly with a technic as simple as that described by the authors no case of lymphoblastoma can be said to be thoroughly studied unless repeated sternal punctures are made, and I think it will not be long before the procedure will be a routine measure in examinations of patients with that condition.

DR. FRED D. WEIDMAN, Philadelphia: Sternal puncture is a technic which is bound to become a part of complete studies of all dermatoses involving diseases of blood-forming tissue. It may appear to be formidable, but with reasonable care osteomyelitis does not result. In this presentation it was particularly the cutaneous lymphoblastomas which attracted attention to the procedure, but it may also be of value in the purpuras, on which Dr. Peck and his co-workers spoke. A simple procedure like this will doubtless be of greater value in the aggregate than the trephining technic of Dameshek, but the latter will permit the identification of the hematopoietic "pattern," which is impossible with smears from material made available by the puncture technic. Furthermore, in elderly patients there is always more or less atrophy even of sternal marrow, and the material secured by puncture might represent only fatty portions. Indeed, the diagnosis of aplastic anemia has been erroneously made on the basis of examination of the bone marrow when the subject was senile. This point might explain the negative results from puncture in the last two of the authors' cases, as one of the patients was 63 and the other 53 years of age. When the results of sternal puncture are negative and yet other data in the case point strongly to a disease of blood-forming tissue (as in one of the authors' cases, in which Hodgkin's disease was suspected) the puncture should be repeated again and again lest marrow cells which are still functioning be missed. In short, I believe that sternal puncture will be the more valuable procedure for the time being, but as der-

matologists become more and more educated to it, i. e., more and more "sternal bone marrow conscious," eventually they will not be quite satisfied with it and will use the Dameshek technic more and more.

Dr. J. Frank Fraser, New York: A few days ago Dr. Alfred H. Illge gave a demonstration of the technic of sternal puncture on a patient with suspected leukemia in Dr. MacKee's clinic at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, and I am able to corroborate the authors' claim in regard to the simplicity and painlessness of the procedure.

All dermatologists are familiar with a group of dermatoses in cases of which the blood picture is normal—the erythrodermas, for example. These may run a course covering a period of months or even years, a diagnosis being impossible on the basis of either the clinical picture or the histologic picture in the skin. The procedure described by the authors should be a valuable aid in these cases. In regard to the related neoplasms in the lymphoblastoma group, referred to by them, while there is still doubt and disagreement about the status of Hodgkin's disease and mycosis fungoides, the work of Furth and his associates has definitely shown leukemia to be a neoplastic process. Sternal puncture should be made a routine procedure in selected cases, for early diagnosis may mean prolongation of life and relief for the patients.

Dr. Lyle B. Kingery: Dr. Wiedman's suggestion is unquestionably correct. By trephining more material is obtained, and, as I understand, there is a better chance to pick up evidences of pathologic processes which instead of being uniform may be "spotty." So much for the advantages of the Dameshek technic. Its disadvantages are, among others, that the technic is more complicated and that there is a possibility of postoperative hemorrhage. Perhaps the simplicity of the method I have described recommends it, and as we have used it it gives the evidence it is expected to give.

NODULAR DIFFUSE SCLERODERMA

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AND
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MINNEAPOLIS

Scleroderma, as is well known, exists in a circumscribed form (morphea, localized scleroderma, scleroderma *en bandes*) and as a diffuse type (scleroderma diffusum), in cases of which involvement of the hands (sclerodactylia) may be a prominent feature.

Localized scleroderma is a benign process which may heal spontaneously and which does not lead to any disturbance of the organism as a whole, even when the involvement is of wide extent. Ehrmann and Brünauer,[1] who made an exhaustive study of scleroderma, stated that this type may involve a considerable portion of the body though the plaques remain sharply bordered and distinct from one another, a feature to be contrasted to the findings in diffuse scleroderma, in which there are no well marginated plaques.

Diffuse scleroderma is a severe, slowly progressive process which may involve not only the skin but all the connective tissues of the body. As a rule it begins symmetrically and insidiously on the extremities, and early in its course it is characterized by prodromal paresthesias (numbness, tingling or feeling of cold), vasomotor symptoms (diffuse redness, cyanosis or local syncope) and trophic disturbances (wheals, vesicles, rhagades or superficial ulcers). After varying periods of time the fingers become plump and cylindric, losing their contour and becoming pointed. The process extends to the dorsa of the hands and forearms and in an analogous way from the toes up the legs. As the extremities become affected there may be simultaneous or rapidly following involvement of the face, especially of the nose, zygoma and chin. As the condition progresses the skin of the face and neck becomes thickened and smooth, immobility and loss of expression resulting. The process may spread diffusely down the chest, interfering with respiration.

From the Division of Dermatology, University of Minnesota Hospital, H. E. Michelson, M.D., Director.

Read at the Fifty-Ninth Annual Meeting of the American Dermatological Association, Inc., Swampscott, Mass., June 4, 1936.

1. Ehrmann, S., and Brünauer, R.: Sclerodermie, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, p. 717.

Late in the course of the disease the face may appear shrunken and masklike, the nose being short and the cheeks sunken, as if the integument were stretched over the skeleton. On the extremities the bones may be narrowed owing to the tightness of the skin, and the movements of the joints, especially of those of the hands, are frequently limited or lost entirely. Contractures, ankylosis, mutilation of digits and loss of nails on the hands are not uncommon. Involvement of the mucosae and internal organs has been reported.[1]

The surfaces of the lesions in both circumscribed and diffuse scleroderma are ordinarily smooth. Nodular plaques have been occasionally reported in cases of circumscribed scleroderma, the increased volume of the connective tissue (due to hypertrophy) causing the involved foci to become raised above the niveau of the surrounding skin and to present a rough, uneven surface. Nodule formation in cases of true diffuse scleroderma, however, is extremely rare, judging from the number of instances reported in the literature. An unusual example of this type of involvement was recently observed by us and is described in detail in this paper.

No discussion of circumscribed and diffuse scleroderma would be complete without consideration of the condition which Josef Sellei,[2] of Budapest, Hungary, has termed acrosclerosis and has discussed at great length within the past few years. Sellei defined acrosclerosis as a disease characterized by shrinking and contracture of the skin, arising always symmetrically on the hands (or feet) and on the face at the same time and accompanied by certain constant symptoms, such as pallor or cyanosis and pain on exposure to cold. He stated that as the disease progresses the face becomes taut ("mask face"), the mouth smaller and the teeth protruding. The hands become flexed and the fingers at times ulcerated or gangrenous.

We believe that in stating his concept of acrosclerosis Sellei has outlined the cardinal characteristic features of scleroderma diffusum as given in the literature and that the condition he described does not deserve the distinction of being regarded as a new and separate entity. He stated that in acrosclerosis there is involvement of the mucosae and that the disease is frequently accompanied by involvement of the heart

2. Sellei, Josef: (*a*) Die Akrosclerosis (Sklerodactylie) und deren Symptomencomplex nebst neueren Untersuchungen bei Sklerodermie, Arch. f. Dermat. u. Syph. **163**:343, 1931; (*b*) Acrosclerosis (Sclerodactylia, Progressive Scleroderma): Its Relation to True Scleroderma, Urol. & Cutan. Rev. **36**:455, 1932; (*c*) Zur Klinik und Therapie der Sklerodaktylie, progressive Sklerodermia (Akrosklerose), Dermat. Ztschr. **64**:138, 1932; (*d*) Beiträge zur Sklerodermie und Akrosclerosis (Sklerodaktylie), Ferment Therapie, München. med. Wchnschr. **79**: 1625, 1932; (*e*) The Diagnosis of Scleroderma and Acrosclerosis and Some of Their Kindred Diseases, Brit. J. Dermat. **46**:523, 1934.

and aorta, features which have often been observed in true diffuse scleroderma. Sellei's various illustrations of the hands and face in cases of acrosclerosis show nothing which differs from the ordinary concept of diffuse scleroderma with sclerodactylia. Sellei [2e] maintained, however, that ". . . scleroderma and acrosclerosis are two different diseases, distinct from one another, differing in all their clinical characteristics and also in their pathogenesis and therapy."

He defined scleroderma verum as a disease which arises in different parts of the body, beginning with an infiltrative process and sooner or later going into a homogenization stage. He divided the types into the circular form (scleroderma circumscriptum), the ribbon-like form (scleroderma *en bandes*) and the irregular form, which he termed "scleroderma diffusum," characterized by irregular hard plaques of a yellow alabaster-like or (uncommonly) of a bluish brown tint. He expressed the opinion that the sharply marginated borders of these plaques are an important diagnostic point and that the lesions are always asymmetrical. As additional features of "scleroderma diffusum," Sellei stated that there are no trophic disturbances and that the disease may heal spontaneously.

We feel that this description of "scleroderma verum" (Sellei) embodies all the well known characteristics of circumscribed scleroderma as given by all writers on the subject throughout many decades and that Sellei in defining the condition which he designates as "scleroderma diffusum" (a subdivision of "scleroderma verum") has given a perfect description of circumscribed scleroderma (morphea) of wide extent. In fact, the photograph in the *British Journal of Dermatology and Syphilology* [3] illustrating Sellei's concept of scleroderma diffusum is practically identical with an illustration in Ehrmann and Brünauer's [4] monograph exemplifying circumscribed scleroderma. In both of these pictures there is a band of localized scleroderma involving the left breast in a woman.

In reference to the hands Sellei stated that the process in acrosclerosis extends from the fingers up the arms. This point in itself, of course, offers no differentiation from ordinary sclerodactylia. He stated, however, that there may be involvement of the hands in the disease which he terms scleroderma diffusum. He termed these changes sclerodactylia originating from scleroderma. Sellei's illustration of "sclerodactylia in scleroderma," however, fits the usual concept of bandlike circumscribed scleroderma extending down the arm and affecting a part

3. Sellei,[2e] p. 526.
4. Ehrmann and Brünauer,[1] p. 724.

of the hand, an example of which Ehrmann and Brünauer [5] illustrated in their monograph. In ordinary terminology this condition would not be considered sclerodactylia at all.

After having given Sellei's writings due consideration, we have decided that the question of the relationship of acrosclerosis and scleroderma is one of nomenclature. Sellei has termed diffuse scleroderma the condition which other writers have designated as extensive morphea (or in reality circumscribed scleroderma). Moreover, he has given the new name acrosclerosis to the process always known as scleroderma diffusum, in which the changes on the hands have long been known as sclerodactylia.

Without in any way attempting to express a final judgment in the matter, for our interpretation may be incorrect, we feel that if the description of these entities were submitted to an international committee the decision would be as we have interpreted it. Even if one granted, however, that acrosclerosis is an entity apart from the sclerodermas, one would have to admit that the conditions are so closely related that the borderline processes in either group would be identical.

It is not our object to enter into an exhaustive analysis to prove or disprove our belief, and we have defined the conditions as we understand them merely for the sake of clarity. The purpose of this paper is to review the cases of nodular diffuse scleroderma and to report an additional example.

CASES REPORTED IN THE LITERATURE

Several cases have been reported in the literature.

In 1906, Dubreuilh [6] studied an odd dermatosis which he termed *"fibromes miliaires folliculaires; sclerodermie consecutive,"* occurring in a woman aged 44. The patient was first seen in 1904, at which time she complained of an almost generalized eruption of small nodules of nine months' duration, which began on the forearms and spread gradually to the upper portions of the arms, shoulders and neck. On examination it was found that the nodules were practically confluent on the extremities, shoulders and neck, discrete on the upper part of the trunk and absent on the abdomen and back. The individual lesions were white or yellowish white round smooth nodules from 1 to 2 mm. in diameter, firm to the touch and exhibiting no signs of inflammation.

The microscopic examination showed an increase of fibrous tissue, which was most marked about the hair follicles and gradually faded into the surrounding tissues. The elastic fibers and the sebaceous and sweat glands seemed normal. A slight round cell infiltration was present.

Debreuilh noted that the confluence of the small nodules on the upper extremities and face produced an aspect identical with that of diffuse scleroderma. The skin on the arms felt thickened, resistant and tense, while that covering the dorsal

5. Ehrmann and Brünauer,[1] p. 723.

6. Dubreuilh, W.: Fibromes miliaires; sclerodermie consécutive, Ann. de dermat. et syph. **7**:569, 1906.

surfaces of the hands seemed so indurated and stretched that movement of the fingers was extremely limited. The nails were apparently normal. Dubreuilh noted that the resemblance to sclerodactylia was complete.

The skin of the thighs was less intensely involved, although it was thickened by the coalescence of the miliary nodules. In the popliteal spaces the lesions were larger and surrounded by supple integument, while the skin of the lower portions of the legs was brown, tense and indurated.

The facial features appeared drawn and immobile, since the small lines had been obliterated by the pathologic process. Owing to the induration, opening of the mouth was accomplished only with great difficulty. The oral mucosa was not involved.

Reitmann,[7] in 1903, reported a case in which the condition closely resembled that in Dubreuilh's case. A woman, aged 40, had noted the development of little papules on the fingers several years previously. Later the skin of the face and ears seemed thicker than normal.

The skin about the nose and neighboring parts of the cheeks seemed diffusely thickened and of a peculiar, alabaster-white color. There were tiny papules in the region of the nose and on the ears. The lips were sclerotic, so that opening of the mouth was difficult. The skin of the neck was also indurated and studded with small follicular papules.

The skin covering the hands was thickened and showed nodules similar to those on the neck, while on the lower extremities the skin was indurated but no papules were seen.

The mucous membrane covering the right side of the soft palate and uvula showed ectatic blood vessels and fibrotic patches of yellow tint. The buccal mucosa felt sclerotic, and on the right cheek the impressions of the teeth could be seen.

Histologic sections showed a thickening of the cutis with an increased amount of fibrous connective tissue. In some of the larger blood vessels there was proliferation of the intima and even endarteritis. The sweat glands were surrounded by a cellular infiltration.

Reitmann expressed the opinion that the condition in his case was analogous to that in Dubreuilh's case, both clinically and histologically, and that the most likely diagnosis was scleroderma.

Lipschütz,[8] in 1913, reported a case of sclerodactylia with accompanying nodule formation in a woman aged 24 who complained of pain in the joints of three years' duration, which developed after exposure to cold. About six months after the onset of these symptoms there was swelling of the fingers.

At the time of examination the changes in the hands were characteristic of sclerodactylia. In addition there were thick, sharply bordered areas of thickening involving the surface of the first phalanges of the index fingers. On the extensor surfaces of the right ring, middle and index fingers and on the left middle and ring fingers, progressing distally from the first interphalangeal joints, were several tender bean-sized nodules of firm consistency. There were no notable surface alterations and roentgenograms of the hands showed no pathologic changes. There were signs of ischemia of the hands, with associated paresthesias on exposure to cold.

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7. Reitmann, Karl: Ueber eine eigenartige, der Sklerodermie nahestehende Affektion, Arch. f. Dermat. u. Syph. **92**:417, 1908.

8. Lipschütz, B.: Knotenförmige Hautverdickungen bei Sklerodaktylie, Dermat. Wchnschr. **57**:851, 1913.

Biopsy of the nodules showed hypertrophy of the connective tissue, endothelial proliferation and adventitial cellular infiltration in the vessels and deeper parts of the cutis.

Lipschütz considered the case one of sclerodactylia with circumscribed fibrous nodosities possibly analogous to those appearing in idiopathic atrophy of the skin.

Bruhns'[9] case of nodular scleroderma occurred in a boy aged 13. The onset, which followed scarlet fever, was characterized by ischemia of the hands on exposure to cold. The skin of the chest and abdomen was stippled by firm, brownish blue, lentil-sized nodules, which were raised from 1 to 2 mm. above the level of the surrounding skin. The left thigh was involved by a typical band of scleroderma, around which were lesions similar to those on the trunk. On the left calf, on the right buttock and in the right scapular region were nodular lesions which were not raised appreciably above the surrounding skin.

The histologic changes consisted of slight but definite thickening of the collagenous tissue in the middle portions of the cutis. The epidermis appeared normal, and there was a lack of inflammatory features. Bruhns expressed the opinion that in this case there was considerable likeness to the condition in Lipschütz' case.

In 1920 Fletcher[10] reported a case of scleroderma with sclerodactylia in a girl aged 11 years who had nodules on the shoulders, knees and thighs which came in crops and the appearance of which was accompanied by an elevation of the temperature to 101 F. In discussing the case Weber stated that he believed the nodules to be of the so-called rheumatic type.

Gray[11] observed a case of generalized scleroderma of four years' duration in a woman aged 26 who also presented lentil-sized subcutaneous nodules seemingly attached to the tendon sheaths, joint capsules and periosteum on the dorsa of the hands and feet and in the region of the hamstring muscles. On both sides of the spine were nodules lying free in the subcutaneous tissue.

On section the lesions were seen to be made up of fibrous tissue with hyaline degeneration. No calcium was present. Weber, as he did in commenting on Fletcher's case, stated that the lesions seemed to be of the rheumatic type.

In 1925 Groedel and Hubert[12] described a case of typical scleroderma which began after the patient had been injured in a severe automobile accident. The patient was a 42 year old man, and by the time he consulted Groedel and Hubert the condition had affected both arms and the face. There were firm, painless, walnut-sized nodules on both forearms, which the observers believed to be similar to those in Bruhns' case.

Bechet[13] in 1927 presented a case of scleroderma with tumefaction before the Manhattan Dermatological Society. The patient had typical diffuse scleroderma with contracted facies and sclerodactylia accompanied by nodules on the flexor surface of the right thumb and over the knees.

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9. Bruhns, C.: Ueber Knotenbildung bei Sklerodermia, Arch. f. Dermat. u. Syph. **129**:178, 1921.

10. Fletcher, H. Morley: Case of Sclerodermia and Sclerodactylia, Proc. Roy. Soc. Med. **14**:40, 1920-1921.

11. Gray, A. M. H.: Generalized Sclerodermia with Subcutaneous Nodules, Proc. Roy. Soc. Med. **16**:107, 1922-1923.

12. Groedel, Franz M., and Hubert, Georg: Ein Fall von Sklerodermie nach Unfall, Wien. klin. Wchnschr. **38**:409, 1925.

13. Bechet: Scleroderma with Tumefaction, Arch. Dermat. & Syph. **15**:508 (April) 1927.

REPORT OF A CASE

History.—E. C., an Irishman aged 71, was referred to Dr. H. E. Michelson by Dr. W. F. O'Connor. The patient stated that as far as he knew his skin was entirely normal until six months previously. At that time he noticed a change in the "feel" of his skin over the entire body. It had become rough, in contrast to the usual smooth texture. Multiple lesions, in general slightly smaller than a split pea, appeared on the forearms, chest, back and sides of the neck and most noticeably on the face in the region of the eyebrows. Approximately at the time these lesions appeared the patient noticed that he was losing the "grip" in his hands and that he was unable to move his fingers as easily as before. At

Fig. 1.—Nodular scleroderma. Note the puckering in the perioral region.

about the same time the skin of the entire body became stiffer than normal, and the scalp became covered with a heavy dry scale. The entire condition, with the exception of slight occasional itching, had been asymptomatic.

The state of the skin did not affect the general health, and the patient felt as well as ever, except for the stiffness in his joints. The course of the entire disease seemed stationary rather than progressive.

The past history was essentially irrelevant. The patient had noted no symptoms of cardiac or pulmonary disease, and the bladder and bowels caused no trouble. He had fractured the right tibia forty-five years previously while hauling logs.

Clinical and Laboratory Examinations.—The patient was well developed and well nourished. The changes in the skin were present on both hands and fore-

arms, on the sides of the neck and on the chest, back, face and scalp. In all these locations the skin was doughy on palpation and less mobile than would be expected in a normal person of similar age. Over the same locations the surface of the skin was nodular. This was most appreciable on the sides of the neck, on the face and on the medial surfaces of the forearms from the styloid process of the ulna to the elbow. Inspection of these areas showed multiple closely arranged achromatic firm nodules varying from 0.5 to 2 mm. in diameter. The largest of these was situated on the face between the eyebrows, and there were innumerable lesions of smaller size on the locations previously mentioned.

The skin of the hands, especially over the fingers, was thin and bound down to underlying structures. The movements of the hands, especially of the fingers, were greatly restricted. The surface of the skin covering the fingers, palms and dorsa of both hands was extremely dry.

Fig. 2.—Sclerodactylia of the hands.

The scalp was also dry and covered by a diffuse adherent seborrheic type of scale. The ordinary senile type of baldness on the crown was present.

The skin of both thighs presented a distinct cutis marmorata. The surface, as in other areas of the body, was definitely drier than normal, but the papules, which were so numerous on the upper extremities, were lacking. Varicosities accompanied by considerable edema were present on both legs below the knees. The skin covering the feet appeared normal in texture, mobility and moisture.

Although thorough examination of the mouth was rendered more difficult by the lack of mobility of the lower jaw caused by the thickened, doughy skin of the face, no lesions could be seen on the tongue or buccal mucosa.

Neurologic and ophthalmoscopic examinations showed no important changes. The Wassermann reaction of the blood was negative, and the urine contained no sugar or albumin. The results of examination of the blood were as follows: The hemoglobin content was 80 per cent; there were 3,800 white cells; the

percentage of polymorphonuclears was 51, that of lymphocytes 35, that of monocytes 3 and that of eosinophils 13. The congo red test for amyloidosis showed that 96.15 per cent of the dye was retained in the blood.

Histologic Examination.—Several biopsy specimens were taken both from the well developed cutaneous nodules and from the areas of smooth but indurated skin. The tissues were fixed in 70 per cent alcohol, embedded in paraffin and sectioned in the usual manner. The observations were, in general, similar in all the sections which were examined.

The epidermis showed no important abnormalities, although in the nodular lesions there was moderate atrophy, probably due to pressure from the underlying process.

The chief changes were in the cutis. In a general survey of the sections one was reminded of a cellular fibroma. The sebaceous and sweat glands appeared

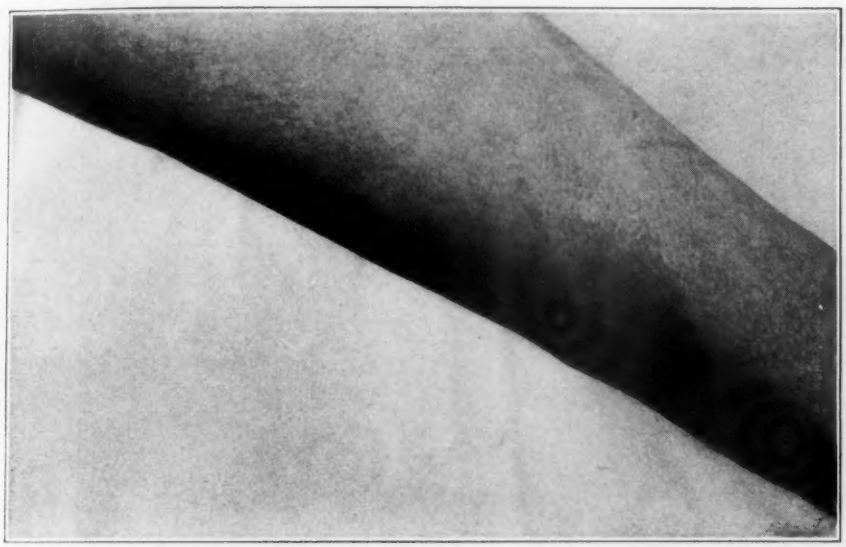

Fig. 3.—Diffuse scleroderma of the arm with small nodules,

normal. The papillary bodies contained numerous dilated blood vessels and were somewhat edematous. Diffusely throughout the entire cutis, from the papillary bodies to the subcutaneous fat, the connective tissue fibers were increased both in thickness and in number, although the impression was gained that in many places they were not compact but separated by edema. At several points there was a tendency toward the formation of whorls. In addition to this increase in connective tissue, there was an inflammatory infiltrate of moderate intensity, distributed especially about the vessels and sebaceous glands and between the connective tissue fibers. Higher magnification showed that the infiltrate was composed largely of small lymphocytes and fibroblasts, although there was a small number of plasma cells and polymorphnuclear leukocytes scattered here and there among the more numerous components of the infiltrate. In a few areas there were small nests of large round or oval cells with pale cytoplasm and vesicular nuclei containing distinct nucleoli. These bore a decided resemblance

to epithelioid cells. The reticular portion of the cutis showed a richness of small blood vessels, while several large vessels with thickened sclerotic walls could be seen near the border between the cutis and subcutaneous fat.

With the Van Gieson stain the entire cutis assumed a yellow or yellowish green color rather than the normal red tint.

In tissues stained by Weigert's method the elastic fibers seemed normal in number and thickness, though they were apparently torn in several areas.

In brief, the chief histologic observations were as follows: richness of blood vessels throughout the cutis with sclerosis of the large, deep vessels; increase in the number and thickness of the connective tissue fibers of the cutis; edema, and a moderate amount of diffusely distributed granulation tissue made up chiefly of lymphocytes and fibroblasts with a few plasma cells, polymorphonuclear leukocytes and cells resembling epithelioid cells.

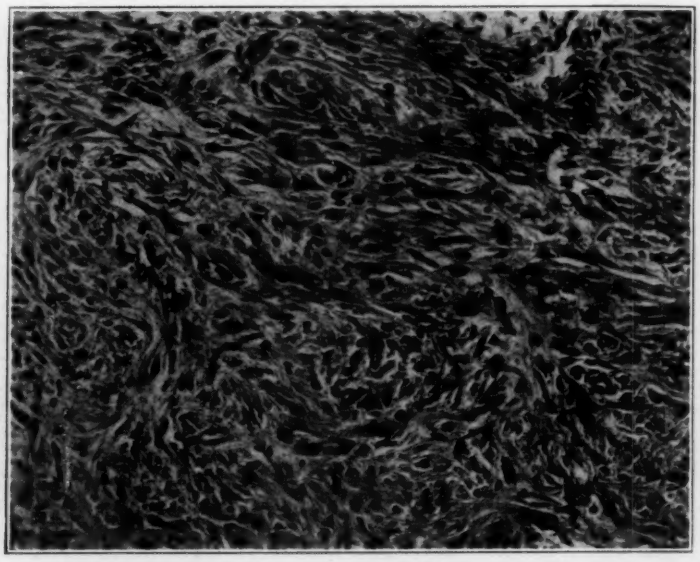

Fig. 4.—High power magnification of a section from one of the nodules, showing increase in fibrous tissue and inflammatory infiltrate.

COMMENT

The patient whom we observed presented several characteristic features of diffuse scleroderma: the doughy, indurated skin; the clawlike, immobile condition of the hands, and the masklike face. The clinical picture seemed identical to that observed by Dubreuilh [6] and Reitmann [7] in their patients, and similar to that reported by Bruhns.[9] Although no photograph accompanies Dubreuilh's article, the appearance in the one illustrating Reitmann's case coincided with the picture in our case. In both of these cases there were indurated skin on the face, sclerodactylia and multiple, firm, small cutaneous nodules.

The condition in the cases of Lipschütz,[8] Fletcher,[10] Gray,[11] Groedel and Hubert [12] and Bechet [13] differed from that in our case in that the

nodules were less numerous and larger. In Gray's case the nodules were apparently attached to the tendon sheaths, joint capsules and periosteum, a feature not present in our case. The final opinion as to the nodules in Bechet's case pointed to a diagnosis of synovial cysts, since gelatinous fluid was obtained on puncture of the lesions.

In Dubreuilh's case histologic examination showed an increase in the fibrous connective tissue (especially around the follicles and sebaceous glands) and an infiltration of round cells in the cutis. In Reitmann's case there were also an increased amount of fibrous tissue, a richness of blood vessels in the cutis—some of which presented a definite endarteritis—and a cellular infiltration (especially about the sweat glands) made up chiefly of lymphocytes and a few plasma and mast cells. The histologic features in both of these cases agreed, in general, with those in the case which we studied. In our case the first impression which was gained from a study of the sections under low magnification was that of scleroderma, since there was a definite increase in the size and number of the bundles of fibrous tissue. On closer scrutiny and under higher magnification the nature of the infiltrate, especially the appearance of the peculiar epithelioid-like cells, was not that commonly seen in scleroderma.

On account of the unusual histologic features sections were sent by Dr. H. E. Michelson to Professors Oppenheim, Kren and Geiger, who studied them. All agreed that, although the histologic picture was odd, the process could be ascribed to the inflammatory stage of scleroderma.

The extraordinary clinical feature in our case which makes it worthy of report was the great number of widely distributed nodules of uniform size throughout the sclerodermatous areas. This gave the integument a cobblestone pavement appearance which was present in every involved part, including the region about the mouth. The significance of this could not be ascertained, but the microscopic observations, although permitting a diagnosis of scleroderma, were decidedly different from any we had previously encountered.

SUMMARY AND CONCLUSIONS

A case of extremely rare manifestations of nodular diffuse scleroderma is reported, and the observations are compared to those in cases of similar conditions described by other observers.

We believe that Sellei's concept of scleroderma diffusum is equivalent to the ordinary concept of extensive morphea, while acrosclerosis (Sellei) is identical with the condition known as scleroderma diffusum throughout the world's literature.

ABSTRACT OF DISCUSSION

DR. FRED WISE, New York: This contribution deals with two separate items—a question of nomenclature and a report of a rare type of scleroderma with nodular formation. With respect to the first item I am thoroughly in accord with the authors. Since I read Sellei's article I have experienced much doubt and confusion with respect to the nomenclature he advocates. My confusion was lessened when I went to Budapest, Hungary, and observed seven or eight of his cases. I saw at once that the condition labeled diffuse scleroderma was designated by him as morphea. In certain cases he called sclerodactylia acrosclerosis and yet said the "skin may be soft." It was pointed out that the name scleroderma cannot be associated with skin that is soft, except in certain terminal phases. Dr. Butler spoke of the different types of scleroderma and sclerodactylia. The other clinical form, morphea, may be widespread and finally fuse, giving rise to widespread scleroderma. I think that Sellei, although his efforts are sincere and well meant, has confused the issue in the way of nomenclature.

The formation of nodules in association with scleroderma is rare, as the authors have said. I am reminded, however, that in acrodermatitis atrophicans one often sees elevated lesions occurring apparently within the niveau of sclerodermatic skin. The histologic picture of these nodules in some ways bears a close resemblance to that of the nodules described by Drs. Butler and Laymon, a plasma cell infiltration, epithelioid cells and an arrangement of elastic fibers differing from that of true scleroderma being present. These differences have been pointed out for many years, especially by Ehrmann, as a superformation in scleroderma-like areas. To my mind it is quite possible that in the disease which was described by the authors the nodular formation is analogous to that seen in acrodermatitis atrophicans. I say this because the histologic picture in many ways resembles that of nodules in that disease.

DR. PAUL A. O'LEARY, Rochester, Minn.: I disagree with the authors and with Dr. Wise in their concept of acrosclerosis. I believe that Sellei is correct in distinguishing the syndrome he has called attention to from diffuse or localized scleroderma. Before I saw the group of cases which he presented in Budapest, I felt that the condition was different from scleroderma, but I often had difficulty in differentiating in cases of some of the borderline manifestations. Accordingly, I have examined patients in whom the involvement was limited to the hands, arms, face and upper portion of the chest, as well as in those with involvement of the trunk and feet, by taking specimens for biopsy from muscle as well as from skin and making studies of the capillaries and an estimation of the vasomotor indexes. If one disregards for the moment the clinical features, it is obvious from these studies that patients with acrosclerosis show reactions different from those exhibited by patients with generalized scleroderma. The histologic changes in the muscles in scleroderma show definite evidence of an inflammatory reaction both in and between the muscle strands, while in acrosclerosis such a reaction is absent. The capillaries differ also in that in scleroderma they are puffy and give the appearance of being dammed back, while in acrosclerosis they are "ironed" out. The Raynaud phenomenon is common in acrosclerosis but less so in scleroderma; it usually precedes the former while in the latter it is a late development. The patients with acrosclerosis showed wide variations, in contrast to those with scleroderma, who had slight if any variation in the vasomotor manifestations. I have studied thirty cases in this manner, and although my concepts are not as yet crystallized because of the marked discrepancies in the scleroderma group, it does seem that acrosclerosis and the Raynaud syndrome are ultimately associated

on the one hand, while scleroderma, chronic fibrositis and dermatomyositis have a similar etiologic relationship.

DR. H. E. MICHELSON, Minneapolis: One of the pleasures of living close to Dr. O'Leary is to be able to disagree with him and thus to create discussion, which usually eventually ends in agreement. I am inclined to think that acrosclerosis and scleroderma are one and the same process and that the extreme degrees of either condition may look a great deal different. I regard the whole problem much as one does the problem of lymphoblastoma, and of course the extreme variation in that condition is well known. I think the most interesting thing about the case described by Dr. Butler is the histologic picture. The section looks suspiciously like fibrosarcoma at first examination; only after prolonged study and with the assistance of Professor Oppenheim and Professor Kren were my co-workers and I able to classify the condition definitely as an unusual manifestation of scleroderma.

DR. JOHN BUTLER: My impression is that in acrodermatitis atrophicans the elastic tissue is chiefly involved, rather than the collagenous tissue as in scleroderma. In Raynaud's disease the changes in the skin never appear in advance of the vascular changes or of gangrene. In so-called acrosclerosis or in diffuse scleroderma cutaneous necrosis may occur, but true gangrene never occurs. I think that Raynaud's disease is in no way related to scleroderma or so-called acrosclerosis.

BILE PIGMENT METABOLISM IN DISEASES OF THE SKIN

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AND
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This study was undertaken to test the possibility that defective hepatic function may be a factor in the production of certain dermatoses. As is well known, the liver is interposed between the gastro-intestinal tract and the general circulation, and one of its functions is to prevent toxic substances from the gastro-intestinal tract from entering the blood stream. This is accomplished, to a large extent, by detoxification, the processes of which include oxidation, reduction and conjugation. Theoretically, therefore, failure of this function of the liver might permit entry of toxic substances into the general circulation and thus lead to their deposition in the skin. That defective hepatic function may be a factor is suggested by the frequent occurrence of cutaneous lesions in cases of diabetes, a disease in which disturbances of hepatic function have been found to be common.[1]

A difficulty of putting the aforementioned possibility to the test of experiment is that there is as yet no satisfactory method for the detection of disease of the liver in an early stage. Another difficulty is the selection of a method from the many procedures available, since the liver has many functions and failure of one of these does not necessarily imply failure of another. From experiences, however, with many thousands of tests in the metabolism laboratories of the Montreal General Hospital and from comparative studies of all the available methods, it appears that one of the earliest measurable effects of hepatic failure is disturbance of bile pigment metabolism, and two of the earliest detectable signs of this disturbance are (*a*) accumulation of excess quantities of bilirubin in the blood and (*b*) excretion of excess quantities of urobilinogen in the urine. As a preliminary procedure, therefore, the bilirubin content of specimens of blood and the urobilinogen

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From the Departments of Dermatology and Metabolism, the Montreal General Hospital.

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1. Rabinowitch, I. M.: (*a*) Brit. J. Exper. Path. **7**:155, 1926; (*b*) **17**:249 (Aug.) 1936.

content of specimens of urine were examined in cases of a variety of diseases of the skin selected at random. The conditions investigated and their incidences are shown in table 1.

METHODS AND STANDARDS

The bilirubin content of specimens of blood was determined by the technic of van den Bergh and McNee.[2] The urobilinogen content of

TABLE 1.—*Conditions Investigated*

Condition	Number of Cases	Units of Bilirubin (Average)
Acne vulgaris	7	0.50
Acne necrotica	1	1.00
Acrodermatitis pustulosa	1	0.80
Alopecia areata and alopecia totalis	13	0.64
Arsenical dermatitis	2	0.40
Bromoderma	2	0.55
Dermatitis herpetiformis	2	0.30
Dermatitis exfoliativa	1	0.20
Dermatitis solare	1	0.20
Eczema (all clinical varieties)	81	0.64
Eczema seborrhoeicum	4	0.62
Epidermophytosis	8	0.74
Erosio interdigitalis blastomycetica	1	0.60
Erythema induratum	2	1.45
Erythema multiforme	1	0.60
Erythema toxicum	1	0.50
Leukoplakia	1	1.00
Leukaemia cutis	1	0.20
Lichen planus	4	0.50
Lichen planus hypertrophicus	1	0.40
Lymphoblastoma	1	0.50
Oidiomycosis	1	0.40
Paraffinoma	1	0.40
Pityriasis rosea	1	0.40
Pruritus (generalized)	4	0.50
Pruritus ani	2	0.90
Psoriasis	49	0.60
Purpura simplex	1	0.40
Pyoderma	1	0.30
Rosacea	3	1.00
Scabies	1	0.50
Sycosis barbae	2	0.25
Syphilis	2	0.30
Urticaria	4	1.00
Urticaria pigmentosa	1	0.50
Vitiligo	2	0.50
Xanthelasma	2	0.40

specimens of urine was estimated by the method of Wallace and Diamond.[3]

Bilirubin is a normal constituent of human blood. It now appears to be definitely established, from extensive data, that the bilirubin con-

2. van den Bergh, H. H., and Snapper, I.: Deutsches Arch. f. klin. Med. **111**:540, 1913. McNee, J. W.: Brit. M. J. **1**:716, 1922; Quart. J. Med. **16**: 390, 1923.

3. Wallace, G. B., and Diamond, J. S.: Significance of Urobilogen in Urine as Test for Liver Function, with Description of Simple Quantitative Method for Its Estimation, Arch. Int. Med. **35**:698 (June) 1925.

tent of the blood of normal persons ranges between 0.2 and 0.5 units or between 0.08 and 0.2 mg. per hundred cubic centimeters of plasma. It is also generally accepted that in the absence of biliary obstruction and hemolysis excess quantities of bilirubin in the blood are due to hepatitis.

Urobilinogen is a normal constituent of human urine, but the amount normally present is small. With the technic which they have described, Wallace and Diamond,[3] using the aldehyde reaction described by Ehrlich, have found that the amount of urobilinogen in normal urine is generally such that the pigment is barely detected when the reagent is applied to urine which has been diluted with 9 parts of water (1:10 dilution). Positive reactions are uncommon when normal urine is diluted with more than 19 parts of water (1:20 dilution). In specimens of urine from 72 of 75 students examined in the morning Wallace and Diamond were unable to detect any urobilinogen in such dilutions. Of 50 specimens of urine from students examined in the afternoon, only 2 were found to have detectable quantities of urobilinogen when 1:20 dilutions were used. Marcussen and Hansen [4] reported somewhat similar experiences in studies of the urines of normal persons with the fluorescence method for detection of urobilinogen. In a routine study of the urines of 1,000 ambulatory patients Wallace and Diamond [3] found that when dilutions greater than 1:20 were used urobilinogen was detected in the urines of only about 10 per cent, and the excess quantities of urobilinogen found in these specimens could easily have been due to the pathologic conditions affecting the respective patients. This fits in with the many thousands of experiences with this test in the metabolism laboratories of the Montreal General Hospital. On the basis of all the combined data, therefore, it may be reasonably accepted that in the vast majority of cases when urobilinogen is detected in urine by the aforementioned test, dilutions greater than 1:20 being used, the excess quantities are due to disease.

COMMENT

A summary of the different diseases investigated and the average amounts of bilirubin which were found in the specimens of blood are given in table 1. In tables 2 and 3 are recorded the data on bilirubin and urobilinogen in the group as a whole and also the relationship found between the disturbances of the metabolism of these bile pigments and the disturbances of dextrose tolerance.

It will be observed (table 1) that, except for eczema and psoriasis, the number of cases of any one of the conditions investigated was small. The data, therefore, except for these two conditions, are of limited significance. It will be noted, however, that in fifteen of the

4. Marcussen, S., and Hansen, S.: J. Biol. Chem. **36**:381, 1918.

thirty-seven conditions, the *average* amounts of bilirubin found were in excess of the generally accepted normal.

Table 2 shows that hyperbilirubinemia (0.6 units or more) was found in 107 of the 216 cases (an incidence of 49.5 per cent). That this high incidence was not accidental is suggested by dividing the cases into two groups, namely, (*a*) those in which blood sugar time curves were also obtained and (*b*) those in which this test was not done. It

TABLE 2.—*Bilirubin Content of the Blood in Cases of Cutaneous Conditions.*

Units of Bilirubin	Total Number of Cases	Blood Sugar Time Curves		
		Number of Cases	Positive	Negative
0.5	109	67	40	27
0.6	29	26	12	14
0.7	11	9	4	5
0.8	31	26	13	13
0.9	8	8	4	4
1.0	20	15	6	9
1.1	..	..	..	..
1.2	..	..	..	..
1.3	..	..	..	..
1.4	..	..	..	..
1.5	3	2	1	1
2.0	4	3	2	1
2.5	1	1	1	..

TABLE 3.—*Urobilinogen Content of the Urine in Cases of Cutaneous Conditions*

Urobilinogen Dilution	Total Number of Cases	Blood Sugar Time Curves		
		Number of Cases	Positive	Negative
1:10	62	45	29	16
1:20	9	8	3	5
1:25	9	6	1	5
1:33	4	3	2	1
1:50	26	21	10	11
1:66	2	0	0	0
1:100	37	26	11	15
1:125	16	11	5	6
1:150	3	2	1	1
1:166	13	11	5	6
1:200	11	11	6	5
1:250	10	8	4	4
1:333	2	2	2	
1:500	1	0	0	
1:1000	1	1	1	
1:1500	1	1	1	

will be noted that of the 157 cases in which blood sugar time curves were obtained, hyperbilirubinemia was found in 90 (an incidence of 57.3 per cent), which fits in with, and is even slightly higher than, the incidence of hyperbilirubinemia in the series as a whole.

Studies of the amount of urobilinogen were made in 207 of these cases, and it will be noted (table 3) that excess quantities of this pigment (in dilutions greater than 1:20) were found in 136 cases (an incidence of 65.7 per cent). That this high incidence was not accidental is also suggested when the cases are divided into the aforemen-

tioned two groups, namely, those in which blood sugar time curves were obtained and those in which blood sugar time curves were not obtained. It will be noted that of the 156 cases in which blood sugar time curves were obtained, excess quantities of urobilinogen were found in 103 (an incidence of 66 per cent), which fits in also with the percentage of cases in the series as a whole.

It should be observed that there was no reason to suspect the presence of an excess amount of pigment in any of these cases, as in none of them was the history suggestive of biliary obstruction, hemolysis or hepatitis. Therefore, there appears to be no doubt that disease of the liver is common in persons with cutaneous lesions.

The experiences with blood sugar time curves are of interest. It will be noted (table 2) that of the 157 cases in which blood sugar time curves were obtained, indications of disturbance of carbohydrate metabolism were found in 83 (an incidence of 52.8 per cent), and that of these 83 cases, hyperbilirubinemia was found in 43 (an incidence of 51.8 per cent), whereas of the 74 cases in which no disturbance of carbohydrate metabolism was detected in 47 (an incidence of 63.5 per cent) there was an excess of bilirubin in the blood. Therefore, though the disturbances of carbohydrate metabolism were common, no relationship was found between the disturbance and the metabolism of the liver with respect to bile pigment.

The experiences were somewhat similar with the urobilinogen test. It will be noted (table 3) that of the 156 cases in which blood sugar time curves were obtained, disturbances of carbohydrate metabolism were found in 81 (an incidence of 51.9 per cent) and that in 49 of these 81 (an incidence of 60.5 per cent) there was an excess of urobilinogen in the urine; whereas, of the 75 cases in which there were no signs of disturbance of carbohydrate tolerance, in 54 (an incidence of 72 per cent) there was an excess of urobilinogen in the urine.

In order to compare the degrees of disturbance of hepatic function in cases of these conditions of the skin with those found in cases of diabetes mellitus (table 4), a reproduction from another report[1b] is incorporated here. It will be noted that in cases of diabetes mellitus the incidence of hyperbilirubinemia was 27.4 per cent and that the percentage of cases in which an excess of urobilinogen was present was 27.5 also; whereas, in cases of cutaneous conditions the incidence of hyperbilirubinemia was 49.5 per cent and the proportion of cases in which an excess of urobilinogen was present in the urine was 65.7 per cent.

It will be noted (table 1) that there were 81 cases of eczema, a number reasonably large for interpretation of data. In tables 5 and 6, therefore, are recorded the excess quantities of bilirubin and urobilinogen and their incidence in these cases. In several of them the condition

was due definitely to external irritants, and in several there was also impairment of hepatic function. Of these 81 cases, hyperbilirubinemia was found in 44 (an incidence of 54.3 per cent), and of 79 cases in which the urobilinogen content of the urine was estimated, excess quantities of this pigment were found in 54 (an incidence of 63 per cent).

TABLE 4 (*Rabinowitch* [1b]).—*Bilirubin Content of Blood and Urobilinogen Contents of Urine Among Diabetic Patients in the Clinic for Diabetes at the Montreal General Hospital.*

(3,000 analyses: cases of jaundice and of suspected jaundice excluded)

Bilirubin		Urobilinogen	
Units	Number	Units	Number
—0.5	2,178	Absent	0
0.6	256	—1:10	1,375
0.7	132	1:16	457
0.8	121	1:20	342
0.9	81	1:25	182
1.0	109	1:33	123
1.1	26	1:50	171
1.2	19	1:100	90
1.3	8	1:125	82
1.4	7	1:150	63
1.5	16	1:166	8
1.6	2	1:200	19
1.7	1	1:250	42
1.8	6	1:133	24
1.9	1	1:500	8
2.0	9	1:1000	12
2.1	8	1:1000+	2
2.2	3		
2.3	4		
2.4	2		
2.5	11		

TABLE 5.—*Bilirubin Content of the Blood in Cases of Eczema*

Units of Bilirubin	Total Number of Cases	Blood Sugar Time Curves		
		Number of Cases	Positive	Negative
0.5	37	27	18	9
0.6	11	9	4	5
0.7	3	3	1	2
0.8	18	17	6	11
0.9	3	3	..	3
1.0	5	4	3	1
1.5	1	..	..	..
2.0	3	3	2	1
2.5	..	..	..	..

The data on the sugar content of the blood are of interest here. In tables 5 and 6 are also recorded the blood sugar time curves which were obtained in the cases of eczema. It will be noted that of the 32 cases in which the curves were normal, in 23 (an incidence of 71.9 per cent) there was an excess of bilirubin, whereas, of the 34 cases of disturbances of carbohydrate metabolism, in 16 (an incidence of 47 per cent) there was hyperbilirubinemia. No parallelism, therefore, was found between the disturbances of carbohydrate metabolism and the hyperbilirubinemia. This also applies to the data on urobilinogen. Of

the 32 cases in which the curves were normal, in 23 (an incidence of 71.9 per cent) there was an excess of urobilinogen in the urine, whereas of the 31 cases in which a disturbance of dextrose tolerance was present, in 21 (an incidence of 67.7 per cent) there was an excess of this pigment.

TABLE 6.—*Urobilinogen Content of the Urine in Cases of Eczema*

Urobilinogen Dilution	Total Number of Cases	Blood Sugar Time Curves		
		Number of Cases	Positive	Negative
1:10	23	18	10	8
1:20	2	1	..	1
1:25	5	5	1	4
1:33	3	2	1	1
1:50	5	5	3	2
1:66	..	..	..	..
1:100	19	15	8	7
1:125	6	5	2	3
1:150	3	2	1	1
1:166	3	3	..	3
1:200	3	3	2	1
1:250	4	3	2	1
1:333	1	1	1	..
1:500	2	..	..	..

TABLE 7.—*Bilirubin Content of the Blood in Cases of Psoriasis*

Units of Bilirubin	Total Number of Cases	Blood Sugar Time Curves		
		Number of Cases	Positive	Negative
0.5	24	11	8	3
0.6	9	9	4	5
0.7	3	2	1	1
0.8	5	5	3	2
0.9	2	2	1	1
1.0	5	4	0	4
2.0	1	0	0	0

TABLE 8.—*Urobilinogen Content of the Urine in Cases of Psoriasis*

Urobilinogen Dilution	Total Number of Cases	Blood Sugar Time Curves		
		Number of Cases	Positive	Negative
1:10	16	11	7	4
1:20	3	3	2	1
1:25	..	..	..	..
1:33	2	..	..	..
1:50	6	6	3	3
1:66	1	..	..	..
1:100	7	4	1	3
1:125	4	1	1	..
1:150	..	..	..	..
1:166	3	2	1	1
1:200	..	..	..	..
1:250	3	3	2	1
1:333	1	1	1	..

In tables 7 and 8 are recorded the data obtained in cases of psoriasis. Of the 49 cases, hyperbilirubinemia was found in 25 (an incidence of 51 per cent), and of the 46 cases in which the urobilinogen content was estimated, excess quantities were found in 27 (an incidence of 58.7 per cent). Again, as in the case of eczema, no parallelism was found

between disturbance of carbohydrate metabolism and impairment of hepatic function. Thus, of the 16 cases in which the curves were normal, in 13 (an incidence of 81.2 per cent) there was an excess of bilirubin, whereas of the 17 cases in which the curves were abnormal, in 9 (an incidence of 52.9 per cent) there was an excess of that pigment. Again, of the 13 cases in which the curves were normal, an excess of urobilinogen was found in 8 (an incidence of 61.5 per cent), whereas of 18 cases in which the curves were abnormal, in 9 (an incidence of 50 per cent) there was an excess of this pigment.

SUMMARY

Though, with few exceptions, the excess of bilirubin and urobilinogen found in these cases was undoubtedly slight, the combined data, we believe, justify the *statistical* conclusion that impairment of hepatic function is common in cases of diseases of the skin. It should be noted that excesses of bile pigment were found in cases of conditions known to be due to an external irritant or to a well recognized infection. The reactions in these cases may have been entirely local. In view, however, of the disturbances of hepatic function in these cases, the possibility must also be considered that impairment of hepatic function not only may permit toxic metabolic products to reach the skin but may so lower the resistance of the skin as to enhance the action of local irritants and infections. Finally, another possibility which must be considered, and which can be excluded only by accumulation of more data and proper statistical analysis, is that impairment of hepatic function may be the result, rather than the cause, of dermatoses. The only purpose of this brief report is to draw attention to the high incidence of disturbances of the liver found in cases of lesions of the skin and to the possibility of a new method of approach to the study of such lesions.

Miss Helen Hyman assisted in the collection and assortment of the data on which this report is based.

ABSTRACT OF DISCUSSION

DR. JOSEPH V. KLAUDER, Philadelphia: Any experimental or laboratory investigation of that important disease eczema is worth while. This study shows expenditure of considerable time and effort in study in that field. The authors found the bilirubin content of the blood above normal in 45 per cent of cases of eczema and in 50 per cent of cases of psoriasis. Their findings raise the question: What rôle does abnormal hepatic function play in the causation of eczema and psoriasis? The authors do not conclude that their findings necessarily indicate the etiology of eczema. Every one realizes the difficulty in connecting abnormal biochemical reactions in cases of eczema with the etiology of the condition. One cannot, for example, conclude that because a patient with eczema has a focus of infection or a large amount of uric acid in the blood one of these factors necessarily causes eczema. The concept of eczema has not changed much since Hebra expressed it about a hundred years ago. It is now known, however, that

the mineral metabolism of the skin, especially the ratio of calcium to potassium, is apparently concerned in disturbing the irritability of the skin. Eczema is a change in the irritability of the skin and represents a pathologic process in which the cutaneous neurocellular mechanism is out of equilibrium.

The skin is a complex organ performing many functions; it is a storehouse of organic and inorganic substances, rich in nerve supply, interrelated with the endocrine glands and influenced by external and internal factors and by the emotional state of the person. The systemic causes of eczema cannot be visualized or expressed in terms of a single pathologic condition. Normal functioning of an organ is dependent on a balance of physiochemical processes and an interplay of other factors. Any deviation from the normal, it becomes reasonable to assume, may have far reaching effects in altering the balance that maintains the normal reactivity of the skin. In this broad view of the etiology of eczema it becomes reasonable that there is a relationship between hepatic dysfunction and a change in the irritability of the skin which results in eczema.

Studies of the causes of eczema have been approached from different angles. The study of Jeffrey Michael is to be recalled. He challenged the view that a large amount of uric acid in the blood was a causative factor in cases of eczema and based his opinion on the fact that he administered uric acid to patients with eczema without causing an aggravation of their disease. This was an attempt to express the cause of eczema in too simple a way.

One can discuss the relation of high bilirubin content of the blood to psoriasis only in a broad way. Brown and I have reported an abnormally high sulfur content in psoriatic skin (ARCH. DERMAT. & SYPH. **34**:568 [Oct.] 1936).

Other evidence of disturbance of sulfur metabolism in patients with psoriasis has been reported. Glutathione, a sulfur-containing compound present in the skin, is an essential constituent of physiologic tissue concerned in biologic oxidation-reduction phenomena. There is evidence that the pathogenesis of psoriasis concerns the oxidation-reduction mechanism of the epithelial cell, a view championed by Van Kerkhoff. If dysfunction of the liver plays a rôle in psoriasis it doubtless does so through disturbance of sulfur metabolism.

DR. HERMAN SHARLIT, New York: I wish to congratulate the authors for their courage in attempting to correlate cutaneous manifestations with the function of an organ so complex as the liver. Because of the multiphasic character of hepatic function it has become necessary to evaluate this function by way of a whole group of tests, including features of carbohydrate, protein, fat and bile pigment metabolism. In view of this it seems to me that it would be difficult to arrive at an adequate conclusion as to normality of function in individual cases. It is not to be expected that normal persons would necessarily come within the range of accepted normality in all the phases of measurable function of this organ. In other words, abnormality in terms of any one given functional test may as likely as not be a measure of normality in the person tested. Furthermore, in the study of hepatic function one must give due consideration to the gastro-intestinal tract when it plays a definite part in the mechanism under consideration. This is particularly true of bile. The bile goes into the intestinal tract, and then its derivatives must be resorbed to be again worked over by the liver for bile formation. The study of features of sugar metabolism as applicable to hepatic function, on the other hand, is less susceptible to the complicating phase of enteric activity. Then, too, functional tests are always under the blight of possible faulty chemical technics. I am reminded of that point by my recent experience in studies of indole metabolism, which also involves hepatic function. In making those studies I early discovered the need for a revision of the methods for indoxyl measurements before acceptable metabolic studies could be made.

I think it is an established clinical experience that if functional tests are done on sick persons and if those tests are sufficiently sensitive and the normal range is sharply outlined, subnormality of function is found to be the rule. In short, clinically sick persons, be their disease dermatologic or other, appear to be "sick all over," that is to say on the basis of statistics functional tests of all kinds place clinically sick persons in the group of those who are functionally subnormal.

I realize that the authors understood these difficulties in the studies of eczema and psoriasis which they made. I feel that this type of work is necessary and that when more is known about the particular elements involved in eczema and psoriasis efforts of this kind will take on more meaning.

Dr. E. William Abramowitz, New York: This paper is extremely interesting. My co-workers and I have been encountering a type of generalized eruption which may be roughly described as an eczema that is unusually persistent and recalcitrant to treatment. When patients with this condition are hospitalized they show considerable improvement, but there is a prompt recurrence of the eruption when they return to their usual environment. No definite causative factors can be discovered. Because some of these patients have been found to have latent disease of the biliary tract I have treated them with biliary drainage along the lines suggested by Dr. Frank Smithies, of Chicago, and Dr. Samuel Weiss, of New York. This has often been followed by marked improvement of the cutaneous condition.

Dr. Marion B. Sulzberger, New York: I wish to say that it is unfortunate that when one hears the term "eczema" one has no idea exactly what is meant or which diseases are included and which are excluded by the particular observer. "Eczema" may refer to an eruption appearing in the folds (intertrigo) of the body; it may refer to an atopic dermatitis; it may be applied to a contact dermatitis, to a circumscribed lichen simplex, or it may be used to designate many and various other dermatoses, depending on the author. It is certain that under the term eczema most dermatologists and most authors are today including a variety of entirely different cutaneous manifestations, and it is most unlikely that these probably essentially unrelated dermatoses are all based on disease of the liver. For this reason it seems to me that the other possibility mentioned should be seriously considered. As Dr. Sharlit so aptly said, when one organ of the body is affected by any illness, the others are also almost inevitably involved. It is possible, therefore, that the disturbance of bile metabolism is a result of the cutaneous involvement. This hypothesis is susceptible of experimental approach. For example, a determination of urobilin and of urobilinogen could be carried out on a group of volunteers who would then allow the production of an experimental dermatitis (eczema!) through sensitization to poison ivy, for example, or to dye intermediates such as dinitrochlorbenzene (to which almost 100 per cent of persons can be sensitized). If the results of a subsequent determination of bile constituents differed from the findings at the first determination and if the second determination showed a pathologic change, it might be concluded that the hepatic impairment was a result of the experimental dermatosis.

Dr. J. F. Burgess, Montreal, Canada: I appreciate the discussion. We tried to show the presence of disturbance of hepatic function in a series of cases selected at random. We cannot, on the basis of our findings, draw any too definite conclusions as yet. As Dr. Stokes said yesterday, there are many factors which, working together, result in disease, and we thought that a disturbance of hepatic function might be one of the contributing causes in some of these dermatoses.

In reply to Dr. Sulzberger, under the heading "eczema" are included conditions of an exogenous character, due to external irritants, "endogenous" eczema and "disseminated neurodermatitis."

Clinical Notes

TREATMENT OF RADIODERMATITIS IN THE HYPERKERATOTIC STAGE

Preliminary Report

HERMAN GOODMAN, M.D., NEW YORK

Hyperkeratosis is a phase of radiodermatitis. It presents certain problems in therapy which need to be mentioned only because no mode of treatment has been universally accepted. Some years ago the use of a poultice of linseed was proposed, and more recently application of the leaf of Aloe vera or of a jelly prepared with it was advocated.

As a result of a study of saponification and emulsification it occurred to me that an emulsion of oil in water would be a satisfactory treatment for certain forms of scaling and infiltration. Such an emulsion was prepared, modern emulsifying agents being used, and the results on two patients treated with the preparation were so gratifying that two surgeons who had patients on whom an operation was to be performed or in treatment of whom operation was ill advised because of infiltration of radiodermatitis were enabled to delay operation or to perform it.

Two physicians who had radiodermatitis of the hands were treated with the emulsion. One physician who had an infiltrating scar and hypertrophy also used it.

REPORT OF CASES

CASE 1.—M. H., a man aged 44, presented radiodermatitis, hyperkeratosis and ulceration of several years' duration in May 1934. He had been treated for hyperthyroidism in 1919. He had received twelve roentgen treatments at monthly intervals. The redness did not begin until one year after completion of the course; this was noted as being unusual and was classed as a belated reaction.

The eruption and ulceration were first noted in 1927. Scaling and destruction became marked despite treatment. Itching was intense and led to bleeding and further local injury. Temporary relief was obtained with creams containing hydrous wool fat and with ointments of various kinds. In 1934 the skin of the neck was stiff and unyielding. The patient wore oversize collars but was unable to turn his head. He wished to have the defect repaired by a plastic operation, but the surgeon preferred to await results of other forms of treatment. Since 1934 the patient had used various medicaments including the leaf of Aloe vera. In June 1935 he began to use the emulsion of oil in water and noted softening, a decrease in itching, scaling and ulceration and greater ease in moving the head. There were less irritation and less desire to "claw" or "dig into" the affected area.

CASE 2.—A. H. C., a woman, presented radiodermatitis, hyperkeratosis and ulceration which had appeared after treatment for hyperthyroidism according to the usual technic. After a few years the symptoms of radiodermatitis appeared. The patient had been treated repeatedly without result. The condition was so irritating that she asked a surgeon to remove the involved area. The surgeon

wished to await the result of other treatment, and the patient tried various medicaments, including a cream containing aloe.

Since January 1936 she has been using an emulsion of oil in water, and the skin has become much softer; the tension has been relieved, and the patient is able to turn and move her head with ease. The skin has become pliable, and the scaling has diminished.

COMMENT

It is obvious that the number of patients who received the treatment is too small to justify any conclusion, yet the favorable results obtained seem to make it desirable to make the treatment more generally available.

METHOD OF PREPARATION AND USE

The method of preparation is as follows:

Four parts of triple-pressed stearic acid and 1 part of hydrous wool fat are melted, care being taken to avoid scorching the mixture, and added to a warmed mixture of 1 part of triethanolamine and enough water to make 100 parts. The temperature should never be above 60 C. The two mixtures are to be stirred slowly, preferably with a mechanical agitator until, after they have passed through a gummy stage, a creamy liquid is formed. If the preparation is agitated too severely there is much froth; this should be avoided.

The emulsion is patted on the area of the hyperkeratotic raidodermatitis as frequently as the exposure of the part permits and dried in situ.

Minor Notes

PATCH TESTS WITH THERAPEUTIC AGENTS

JOSEPH GOODMAN, M.D., AND MARION B. SULZBERGER, M.D., NEW YORK

The frequency with which dermatologists are faced with the problem of treating patients who are or may be sensitive to therapeutic agents makes it highly desirable for those who practice this specialty to be prepared to make patch tests with all the substances which are commonly used in treatment. By being prepared to make such tests dermatologists may often save much time and avoid many mistakes.

Particularly in patients with chronic or recurrent dermatoses we have found routine patch testing with the substances named in the list to be of great aid in future management. In some instances sensitivity which was not suspected has been uncovered. For example, one patient with an atopic dermatitis was relieved of an eruption on his fingers when hypersensitivity to resorcinol was discovered by means of the routine tests. He had been using a scalp lotion containing resorcinol for many months before he was tested. In other instances, when patients present themselves who have eruptions which have obviously been made worse by treatment it is almost essential to make patch tests with therapeutic agents immediately, so that the proper treatment may be instituted without delay and without the danger of using substances to which the patients may be hypersensitive.

Since we have found this group of therapeutic agents (as well as the group for the routine investigation of the contact type of sensitivity, which we have described elsewhere[1]) to be extremely useful for testing patients both in the office and at clinics, we think it worthwhile to publish this list of substances and the concentrations in which they may be used without primary irritant effect.[2]

1. Crude coal tar, 10 per cent in petrolatum
2. Juniper tar (oil of cade), 10 per cent in petrolatum
3. Rectified oil of birch tar, 10 per cent in petrolatum
4. Naftalan (a tar distilled from Russian petroleum, containing about 3 per cent of a hard soap), 10 per cent in petrolatum
5. Sulfonated bitumen (ichthyol), 10 per cent in petrolatum
6. Solution of coal tar N. F., 10 per cent in water
7. Peruvian balsam, 10 per cent in petrolatum
8. Resorcinol, 10 per cent in water
9. Chrysarobin, 1 per cent in petrolatum
10. Vioform, 5 per cent in petrolatum

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1. Sulzberger, M. B., and Goodman, J.: Description of a Technic for the Study of Allergy in Eczematous and Eczematoid Dermatoses, Journal-Lancet **56**:134 (March) 1936.

2. Substances for which no concentration or base is given are applied full strength for testing.

11. Arning's tincture (anthrarobin 3 per cent, tumenol ammonium 6 per cent and glycerine 6 per cent, in spirits of ether)
12. Precipitated sulfur, 10 per cent in petrolatum
13. Compound ointment of benzoic acid N. F. (Whitfield's ointment)
14. Benzoic acid, 10 per cent in petrolatum
15. Salicylic acid, 10 per cent in petrolatum
16. Ammoniated mercury, 10 per cent in petrolatum
17. Ammoniated mercury, 5 per cent, and salicylic acid, 5 per cent, in petrolatum
18. Mercurochrome, 2 per cent in water
19. Boric acid, 10 per cent in petrolatum
20. Menthol, 1 per cent in petrolatum
21. Thymol, 1 per cent in petrolatum
22. Ethyl aminobenzoate (benzocaine), 10 per cent in 70 per cent alcohol
23. Nupercaine, 1 per cent in petrolatum
24. Potassium permanganate, 0.1 per cent in water
25. Trinitrophenol (picric acid), 10 per cent in water
26. Butesin picrate
27. Oil of bergamot
28. Rose water ointment U. S. P.
29. Olive oil
30. Wool fat U. S. P. (anhydrous lanolin)
31. Petrolatum U. S. P. (yellow petrolatum)
32. Glycerin U. S. P.

A few substances which are not ordinarily employed in therapy but which are often contained in ointments or lotions used before the patient is seen are included in the list (butesin picrate, trinitrophenol, oil of bergamot). In testing with boric acid and ammoniated mercury it is important to avoid the "National Formulary" ointments, for in addition to petrolatum they contain 5 per cent hydrous wool fat and 5 per cent white wax.

It will be found by those who use this list of substances for tests that 5 per cent ammoniated mercury plus 5 per cent salicylic acid sometimes produces a positive reaction, while each ingredient alone and in 10 per cent concentration produces no reaction.

The significance of this finding is not clear, but knowledge of it has led us to include on the list both compound ointment of benzoic acid N. F. in full strength and the separate ingredients contained in the ointment.

Some dermatologists may prefer to omit certain items given in the list and to include others which they are more accustomed to use in practice. When this is done, it is important to apply the added substances in the maximum concentration in which they are used therapeutically, so that the lesser degrees of sensitivity may be more easily discovered.

It is of course obvious that a negative reaction to a patch test is not an absolute guarantee that the substances tested may be used wih impunity. The possible development of hypersensitivity at a later date and the possible local variations in the sensitivity of different sites, as well as possible spontaneous chronological variations in sensitivity, must be taken into consideration. These are among the factors which may account for the occasional observation of an irritation which ensues in spite of a prior absence of reaction to patch tests.

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Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

ASSOCIATED FACIAL AND INTRACRANIAL HEMANGIOMAS. HARRY M. GREENWALD and JACOB KOOTA, Am. J. Dis. Child. **51**:868 (April) 1936.

This paper deals with the fact that hemangiomas of the brain are often associated with nevi. Two of the most characteristic symptoms of the disease are convulsions and spastic hemiplegia. The entire clinical picture has been termed the neurocutaneous syndrome. In many instances the nevi follow the area of distribution of one, or of all, of the branches of the trigeminal nerve. Not only are the nervous system and the skin involved, but the retina, gastro-intestinal tract and other organs are also affected. The nevi occur practically always on the same side as the cerebral lesion. Roentgen examination of the skull may shown abnormalities due to calcification in the meningeal angioma. Such changes were present in thirty-four of the thirty-nine cases in which the skull was examined roentgenologically. A summary of the data in twenty-four confirmed and in fifty-eight unconfirmed instances of this syndrome is given. Surgical intervention and radiotherapy are the only methods of treatment. In general the prognosis is poor. The authors report a case of their own which occurred in a 5 year old boy.

NELSON PAUL ANDERSON, Los Angeles.

THE EFFECT OF ROENTGEN RAY IRRADIATION ON PLATELET PRODUCTION IN PATIENTS WITH ESSENTIAL THROMBOCYTOPENIC PURPURA HEMORRHAGICA. S. R. METTIER, R. S. STONE and K. PURVIANCE, Am. J. M. Sc. **191**:794 (June) 1936.

In this series of seven patients with essential thrombocytopenic purpura six patients received roentgen irradiation over the spleen and one received irradiation over the long bones. Individual doses consisted of 200 roentgens, and total doses ranged from 1,200 to 3,300 roentgens.

Before treatment the platelet count varied from 10,000 to 40,000 per cubic millimeter. In six patients there was an increase in the number of platelets within forty-eight hours and in some the platelet count reached 500,000 in nine days.

The authors conclude that roentgen irradiation of the spleen in doses of from 200 to 300 roentgens causes an increase in the number of blood platelets in patients with idiopathic thrombocytopenic purpura haemorrhagica.

THE LAG PHASE IN EARLY CONGENITAL OSSEOUS SYPHILIS: A ROENTGENOGRAPHIC STUDY. N. R. INGRAHAM JR., Am. J. M. Sc. **191**:819 (June) 1936.

For his roentgenographic study of children with congenital syphilis, Ingraham selected those who had received little or no prenatal therapy in order to exclude any osseous changes due to treatment.

Analysis of his data indicates that syphilitic osteochondritis becomes roentgenographically evident about five weeks after infection of the fetus has taken place. Likewise syphilitic periostitis could be discovered about four months after infection.

It is his belief that roentgenographic examination of the osseous structures is important in determining the duration of the infection especially in cases in which the serologic reaction is negative. The reaction would probably become positive by the time periostitis had developed.

JAMIESON, Detroit.

CONTROL OF SYPHILIS AND GONORRHEA IN THE SCANDINAVIAN COUNTRIES AND GREAT BRITAIN. C. W. CLARKE, Am. J. Syph., Gonor. & Ven. Dis. **20**:7 (July, pt. 2) 1936.

In each of the countries reported on by the commission, there appears to have been a downward trend in the prevalence of syphilis since the peak in 1919 or 1920. The prevalence of gonorrhea has remained comparatively unchanged.

Several causes are believed to have played an important part in the decrease of syphilis, but it is generally felt that prompt and adequate treatment of the disease in the infectious stage was most important.

In all countries diagnosis and treatment are free to all persons, without economic distinction. In Sweden and Denmark the expense is borne by the state. In Great Britain the expense is shared by the state and local governments. In Norway the expense is for the most part taken care of by a health insurance scheme.

In the Scandinavian countries public health measures for the control of syphilis and gonorrhea are based on the principle that these diseases are communicable and should be dealt with as such. The law requires that cases be reported, obligates patients to receive treatment, provides for hospitalization if necessary, penalizes known transmission of infection and authorizes the finding and bringing under control of all sources of infection and of all delinquent patients.

In Great Britain syphilis and gonorrhea are not reportable and not quarantinable; treatment is entirely voluntary, and the health authorities have no power to intervene for the protection of the public health, even in regard to the most infectious and uncooperative patients.

In the United States the policy and practices more nearly resemble those of the Scandinavian countries, for all the legal powers of those countries to deal with syphilis and gonorrhea as communicable diseases obtain here. However, there are not in the United States free and accessible facilities for the diagnosis and treatment of syphilis and gonorrhea regardless of economic status. The critical problem in this country may be said to be that of overcoming these obstacles and bringing all patients with infectious syphilis and gonorrhea, regardless of economic status, under medical care.

REUTER, Milwaukee.

FACTORS RESPONSIBLE FOR JAUNDICE IN SYPHILIS, WITH SPECIAL REFERENCE TO THE RÔLE OF THE ARSPHENAMINES. R. V. SAGER, Arch. Int. Med. **57**:666 (April) 1936.

The literature on jaundice in syphilis is thoroughly reviewed by Sager. After thoroughly discussing the work that has been done on this subject and considering his own cases, he draws some definite and interesting conclusions.

It is his belief that catarrhal jaundice does not occur in association with definite anatomic syphilis of the liver, and he states that in 0.37 per cent of untreated persons with secondary syphilis a jaundice resulting from the toxic spirochetosis develops.

Jaundice has been observed in greatly increased numbers since the use of the arsphenamines, and it has also been observed in cases of both secondary and tertiary syphilis. As the arsphenamines are hepatotoxic Sager believes them to be responsible for paratherapeutic icterus.

Syphilitic patients with paratherapeutic icterus apparently have a greater tolerance for the arsphenamines, and this is due, in Sager's estimation, to the greater resistance to hepatic poisons developed by regenerated hepatic tissue.

In his opinion it is possible to distinguish paratherapeutic jaundice from epidemic or endemic catarrhal jaundice. Sager also considers it possible that certain infections or toxins may act on the liver in such a manner as to potentiate the effect of the arsphenamines.

LYMPHOBLASTOMA CUTIS: REPORT OF A CASE WITH AUTOPSY. A. S. ROSENFELD and J. V. STAUMFJORD, Arch. Int. Med. **57**:758 (April) 1936.

In the case of lymphoblastoma cutis reported by Rosenfeld and Staumfjord the disease had been present for seven years, and the patient presented an early

stage of exfoliative dermatitis, lymphadenitis and changes in the blood typical of lymphatic leukemia. This diagnosis was confirmed by biopsy. Tumors of the skin and splenic enlargement occurred later on. The total number of white blood cells remained relatively low, varying between 5,000 and 26,000 during a five year period, but the type of cells was unchanged.

In their review of the literature the authors adhere to the recognized grouping of this disease with leukemia, Hodgkin's disease, lymphosarcoma and mycosis fungoides. All these conditions may affect the skin and may or may not be associated with changes in the blood and internal organs.

Differentiation is often impossible. In all cases the disease is eventually fatal, though a complete remission may occur.

COOPERATIVE CLINICAL STUDIES IN THE TREATMENT OF SYPHILIS. CARDIOVASCULAR SYPHILIS: II. SYPHILITIC AORTIC REGURGITATION; ITS TREATMENT AND OUTCOME. H. N. COLE and L. J. USILTON, Arch. Int. Med. **57**:910 (May) 1936.

In the entire group of cases of cardiovascular syphilis syphilitic aortic regurgitation was found in 260 cases, a percentage of 4.1. This complication was observed twice as frequently in Negro as in white patients, the incidence being greatest in Negro males.

In 85 per cent of the cases in which the Wassermann test of the blood was made within ten days of the detection of aortic regurgitation there was some degree of positivity, although the symptom of cardiac involvement was found most frequently from twenty to thirty years after infection. In 62 per cent of the cases in which the spinal fluid was examined it was abnormal.

Attention is called particularly to the fact that in 69 per cent of the cases no previous antisyphilitic treatment had been given. In others irregular treatment had been given in the late stages of the disease.

In cases in which adequate treatment was administered after the discovery of the aortic lesion, duration of life was increased from forty to forty-five months. Adequate treatment in these cases consisted of both an arsenical and a heavy metal.

Treatment of syphilis should be governed by the degree of regurgitation.

Extreme caution is advised in beginning treatment. The therapy should start with administration of heavy metal and potassium iodide, and the arsenicals should be used in small doses; the first dose of neoarsphenamine should be 0.05 Gm.; this is given after the patient has responded to the preceding treatment.

The dose of arsenical can be increased to 0.3 or 0.45 Gm. at weekly intervals if no untoward symptoms develop, and the arsenical can be given in alternate series with the heavy metals.

COOPERATIVE CLINICAL STUDIES IN THE TREATMENT OF SYPHILIS. CARDIOVASCULAR SYPHILIS: III. ANEURYSM; ITS SYMPTOMATOLOGY, DIAGNOSIS, TREATMENT AND OUTCOME. H. N. COLE and L. J. USILTON, Arch. Int. Med. **57**:919 (May) 1936.

Of the seventy-four cases of sacculated aneurysm included in this study, in 50 per cent the condition was found in the period from fifteen to twenty-five years after infection. In a few cases it was found as late as forty years after infection had occurred.

The Wassermann reaction of the blood was positive in 90 per cent of the cases in which the test was made within ten days of the diagnosis, and in 64 per cent of the cases in which lumbar puncture was made within two months of the diagnosis the spinal fluid was definitely abnormal. Of the total number of patients with aneurysm 31 per cent showed a concomitant involvement of the central nervous system.

Before the discovery of the aneurysm 77 per cent of the patients in this group had received no treatment.

The treatment recommended for patients with this type of involvement was the same essentially as that for patients with cardiovascular syphilis, i. e., initial

treatment with potassium iodide and the heavy metals, use of arsenicals in small, gradually increasing doses unless these drugs were definitely contraindicated, and courses of heavy metal and the iodides in the interim.

Adequate treatment increased the length of life from thirty-seven to seventy-five months.

JAMIESON, Detroit.

LATE TOXIC RESULTS, INCLUDING DERMATITIS EXFOLIATIVA, FROM "SLIM" (DINITROPHENOL). J. M. HITCH and W. F. SCHWARTZ, J. A. M. A. **106**: 2130 (June 20) 1936.

Hitch and Schwartz give a complete bibliography and briefly summarize the literature on the early and late toxic effects sometimes resulting from the ingestion of dinitrophenol. The case of a 33 year old woman is reported, in whom after ingestion of 28 grains (1.82 Gm.) of dinitrophenol within a period of two weeks, a combination of several late sequelae was noted. The patient first came under observation because of a widespread exudative, markedly pruritic eczema of eight months' duration. The eruption later changed to a classic generalized exfoliating dermatitis. Incipient cataracts in both eyes and polyneuritis were additional complications. Electrocardiographic studies indicated slight myocardial damage.

THE CHOICE OF BISMUTH OR MERCURY WITH ARSPHENAMINE. A. B. CANNON and J. ROBERTSON, J. A. M. A. **106**:2133 (June 20) 1936.

From a comparative study of the results of treatment of 379 patients with syphilis, Cannon and Robertson state that the salts of both bismuth and mercury have an important place in the antisyphilitic armamentarium. They found that spirochetes disappeared from primary lesions and that the lesions themselves healed more promptly as a result of therapy with bismuth than of that with mercury, but a positive Wassermann reaction reversed earlier when mercury was used in the primary stages of the disease. In cases of secondary syphilis the general cutaneous eruptions, condylomas and mucous patches healed more quickly with mercury than with bismuth while the Wassermann reaction of patients treated with bismuth became negative before that of persons treated with mercury. The incidence of serologic resistance to mercury was twice as large as that of resistance to bismuth, but more relapses occurred with the use of bismuth. Among patients with early syphilis who completed the required first year of regular treatment there was a larger proportion of satisfactory outcomes in the group treated with mercury than in that treated with bismuth. Complications which could be definitely attributed to the heavy metals alone were twice as common with mercury as with bismuth. The incidence of the delayed systemic reactions, such as dermatitis, jaundice and neuritis, in the causation of which both arsphenamine and the heavy metal were presumed to have had a part, was only a little more than half as great in the mercury as in the bismuth group. Cannon and Robertson conclude that mercury gives more brilliant but less uniform results than bismuth, so that in robust patients with a healthy excretory mechanism the body's natural defenses are perhaps more effectively stimulated by the mercurials. For less vigorous patients and for those who do not respond well to mercury preparations, bismuth offers a valuable substitute. Alternating the use of the two metals minimizes the chances of ill effects.

VIABILITY OF BACTERIUM TULARENSE IN HUMAN TISSUES. L. FOSHAY and O. B. MAYER, J. A. M. A. **106**:2141 (June 20) 1936.

Foshay and Mayer report the case of a man, aged 49, who had a sore finger after he dressed a rabbit. High fever, chills, profound weakness and pain limited to the hand and arm were the chief symptoms. Tender swellings occurred at the elbow and in the axilla. The lesion on his finger was ulcerated and pustular, and surrounding purplish engorgement and redness extended up the dorsum of the hand to the wrist. The number of white blood cells was 10,400. An intradermal

test with a suspension of Bacterium tularense gave a moderately positive reaction the next day and a markedly positive reaction forty-eight hours later. A blood serum agglutination test gave partial agglutinations with 1:10 and 1:20 dilutions. Antitularense horse and goat serums were used successfully in treating the patient. Three months after the onset of the disorder the region of the right elbow became smooth, red and tender. This subsided, but the symptoms recurred three weeks later. The swelling became sharply localized in the region of the olecranon bursa. Bact. tularense was found in the fluid aspirated from this bursa. No constitutional symptoms accompanied the bursitis. Foshay and Mayer conclude that Bact. tularense can survive for long periods in certain tissues of cured patients. The ultimate outcome of these bacterial seclusions seems to depend on the solidity of the established bacteriostatic equilibrium.

LEWIS, New York.

OBSERVATIONS ON POISON IVY HYPERSENSITIVENESS IN GUINEA PIGS. FRANK A. SIMON, J. Immunol. **30**:275 (April) 1936.

Simon found that a deficiency in vitamin C inhibited the development of hypersensitiveness to poison ivy in guinea-pigs. He demonstrated a well developed hypersensitiveness within seven days after the first application of the extract. Only application of the antigen to the skin resulted in a hypersensitiveness; intramuscular, intraperitoneal, and intravenous injections did not sensitize the animals. Sensitization of tissues other than the epidermis could not be demonstrated. Passive transfer tests with the serum gave negative results. Excision of the area of skin to which a sensitizing application had been made was ineffective in preventing the development of hypersensitiveness provided the skin was removed from eighteen to twenty-four hours or longer after the sensitizing substance had been applied. Excision of the site before this time prevented the development of sensitization. The method of spread of hypersensitiveness from the site of application of the extract over the surface of the body was investigated, but positive evidence was not obtained. Histologic study of the lesions revealed evidence of an acute inflammatory reaction in both the epidermis and the papillary layer of the corium with considerable necrosis of epidermal cells. This reaction was observed in both a sensitized and a nonsensitized guinea-pig, but the reaction was definitely more marked in the former than in the latter. Attempts to sensitize rats, rabbits and cats to poison ivy were unsuccessful.

CORNBLEET, Chicago.

THE PREVENTION OF ANTHRAX INFECTION IN WOOLEN TEXTILE PROCESSING. IAN G. MACDONALD, J. Indust. Hyg. & Toxicol. **18**:357 (June) 1936.

The occurrence of sporadic cases of anthrax and of a single small epidemic, in a carpet mill led the author to conduct a survey to determine what inhibitory effect the various chemical, thermal and mechanical processes used in manufacturing carpet exerted upon the viability of Bacillus anthracis. Thirty-one of forty-eight cultures of raw wool from nine different lots taken from materials used in the factory shortly after the infections occurred showed B. anthracis. Dust from the floors and dusting machines did not harbor the organism. After they had been scoured and dried the infected wools produced only a feeble growth on culture, and after they had been dyed the wools were uniformly sterile. The author describes a process in which solution of formaldehyde is used for the destruction of organisms which may have survived the processing of undyed wool. The need for prompt attention to minor cuts and abrasions sustained by, and for proper cleansing of the skin of, workers in wool is stressed. Excellent clinical results in treating the infected patients were secured by intravenous administration of antianthrax serum. The excision of the infected area is considered by the author to be contraindicated.

WIEDER, Milwaukee.

THE BACTERICIDAL AND BIOLOGICAL PROPERTIES OF PHENYL MERCURIC SUBNITRATE. K. T. SASANO and E. M. MEDLAR, J. Infect. Dis. **59**:35 (July-Aug.) 1936.

It was found that phenylmercuric subnitrate, besides being a powerful germicide, has the desirable quality of noninterference with antigenic properties or immunologic substances. It is relatively nontoxic. A 10 cc. dose of a 1:1,500 solution caused a rather severe local inflammation at the site of intravenous injection in some instances, but was not accompanied by any apparent systemic reaction.

DIETARY DEFICIENCIES AND RESISTANCE TO INFECTION BY MONILIA. LOIS ALMON, S. B. PESSIN and W. D. STOVALL, J. Infect. Dis. **59**:54 (July-Aug.) 1936.

The authors found no evidence that deficient diets caused an increased susceptibility to infection with species of Monilia. Pneumonia associated with the presence of Monilia in the tissues as occurring in animals receiving a deficient diet could be duplicated in normally nourished controls. The organisms may remain for several days in the digestive tract without producing symptoms or pathologic change. Unless the lungs are diseased or become diseased the organisms do not remain there long. Whether any of the changes in the lungs observed in the experimental animals were caused by Monilia albicans could not be clearly established.

CORNBLEET, Chicago.

COMPLEMENT-FIXATION TEST FOR SYPHILIS. A. GUHA, Calcutta M. J. **30**:719 (June) 1936.

After describing a technic for the complement fixation test for syphilis, the author suggests that a conference of laboratory workers in India be held to discuss the use of a standard method in order that results might be uniform.

LYNCH, St. Paul.

EXCESSIVE PERSPIRATION. A. H. PIRIE, Canad. M. A. J. **34**:301 (March) 1936.

From 1909 to 1935, Pirie treated fifty-seven patients with localized hyperhidrosis by means of roentgen rays. The sites of the excessive perspiration were the hands in twenty instances, the feet in eighteen instances, the axillae in eighteen instances and the face in one instance. In all cases the condition was relieved, and in fifteen in which the patients were followed cure was permanent.

The dose of roentgen rays employed was 1 skin unit (250 roentgens) of unfiltered radiation given once a month for six months. In some instances the irradiated skin became too dry. The axillary hair was usually permanently depilated. Telangiectasia was also a common sequel, and this caused Pirie to exclude patients with facial hyperhidrosis from treatment.

ICHTHYOSIS. L. M. MULLEN, Canad. M. A. J. **34**:430 (April) 1936.

In the case reported by Mullen an ichthyosis of wide extent was present. The cause of death, which occurred when the patient was aged 3 months, was not determined. Two brothers of this patient, one of whom also had ichthyosis, died at the ages of 1 and 6 months, respectively, the cause of death being unknown. Two sisters, aged 5 and 2 years, respectively, were alive and well.

LEWIS, New York.

THE DISTRIBUTION OF INTENSITY IN THE RADIATION FIELD OF THE INFRA-ROENTGEN RAY TUBE. HEINZ BERGER, Dermat. Wchnschr. **101**:1235 (Oct. 5) 1935.

Berger shows that there is a considerable difference in the patterns of radiation intensity between the output of the Siemens and that of the Müller tube. Tables accompany the article.

POSSIBILITY OF INFLUENCING THE EPICUTANEOUS TUBERCULIN REACTION. H. HRUSZEK, Dermat. Wchnschr. **101**:1291 (Oct. 19) 1935.

Hruszek made dilutions of equal parts of old tuberculin and the following substances: (1) physiologic solution of sodium chloride, (2) epinephrine, (3) vitamin C (in the form of cevitamic acid) and (4) histamine in a 1:1,000 dilution. With these dilutions he made patch tests on a series of twenty-three patients, twelve of whom had cutaneous tuberculosis and eleven of whom had other disorders. The results demonstrated the nonspecificity of the tests, and it was noted that histamine and epinephrine increased the strength of the reaction. In tests on another series a 50 per cent dilution of old tuberculin was titrated to a p_H of 3, 5, 7 and 8, respectively. Comparison of the results of patch tests showed that the more acid and more alkaline specimens caused the most marked reactions. The author concludes that the epicutaneous tuberculin test suggested by Nathan and Kallos is not specific for cutaneous tuberculosis.

A NEW METHOD OF TREATING DERMATOSES DUE TO LIGHT. A. B. SELISKY, Dermat. Wchnschr. **101**:1299 (Oct. 19) 1935.

Selisky successfully treated twenty-eight patients with dermatoses due to light by intramuscular injections of a mixture of hydrolysates of a number of glands of internal secretion. Testes, liver, thyroid, anterior pituitary and thymus were hydrolyzed by fermentation with pepsin and pancreatin plus heat. Equal parts of all these hydrolysates were mixed, and from 3 to 5 cc. was injected, the doses being increased gradually. One patient with a dermatosis that was due to heat rather than to sunlight was not benefited. Patients in whom eczema accompanied the dermatosis showed no improvement of the eczema. In many cases the improvement was immediate.

DIAGNOSIS, CLINICAL COURSE AND THERAPY OF LYMPHOGRANULOMA VENEREUM. ALBERT WIEDMANN, Dermat. Wchnschr. **101**:1319 (Oct. 26) 1935.

Wiedmann reports the case of a patient with an ulcerated lesion of the frenum of the penis and associated large lymph nodes which broke down. There was also a papular eruption, and the Wassermann reaction of the blood was weakly positive. Antisyphilitic therapy brought no relief. The Frei reaction was positive, and histologic examination of the gland confirmed the diagnosis. The patient was successfully treated by the usual local applications and administration of a gold preparation.

ACARIASIS SEU DEMODICITIS HOMINIS. M. BATUNIN and IOLKIN, Dermat. Wchnschr. **101**: 1355 (Nov. 2) 1935.

The authors examined material from 138 persons free from cutaneous disease for Demodex folliculorum. They observed the organism in only 5 instances. Examination of material from 107 patients with dermatologic conditions showed Demodex in 24 instances. The patients in this group had desquamative erythematous eruptions of the face, otherwise classified as eczema, rosacea and similar conditions. Batunin and Iolkin concluded that acariasis is more common than is usually believed and that the diagnosis is verified only by microscopic examination. The possibility of infection from a dog or cat is considered. Treatment consists of application of juniper tar and sulfur ointment.

PRACTICAL VALUE OF THE QUICK REACTION FOR THE SEROLOGIC DIAGNOSIS OF SYPHILIS IN OFFICE PRACTICE. ERNST EICKMANN, Dermat. Wchnschr. **101**: 1383 (Nov. 9) 1935.

The citochol test can be readily carried out by the practitioner in his office. The reaction serves as a satisfactory verification of the clinical diagnosis and as a way of ascertaining the progress of therapy. It should, however, be checked by comparison with the Wassermann reaction.

CUTANEOUS CANCER RESULTING FROM TRAUMA. ERHARD RIECKE, Dermat. Wchnschr. **101**:1410 (Nov. 16) 1935.

A lightly pigmented nevus was present under the right eye of a 31 year old man. After typhoid and cholera vaccine were inoculated in the thigh the nevus became active, and a basal cell epithelioma developed. The protective inoculations cannot be considered to be the cause of the malignant change.

CACHEXIA IN MAN FOLLOWING REPEATED INJECTION OF FOREIGN ALBUMIN. WILHELM MILBRADT, Dermat. Wchnschr. **101**:1417 (Nov. 16) 1935.

Milbradt points out that long-continued injections of foreign protein may lead in man as in laboratory animals to generalized cachexia due to protein. The symptoms are motor pareses, paresthesia, general weakness and pain in the sacral region. Experiments with animals have shown that the process is partly inflammatory and partly degenerative. Most of the organs are involved, but the liver and the central nervous system are the first affected. Further experiments showed that the ingestion of liver extract partially protected animals against relatively large doses of a foreign serum.

UNUSUAL DRUG ERUPTION IN AN INFANT CAUSED BY PERNOCTON. RICHARD FRÜHWALD, Dermat. Wchnschr. **101**:1424 (Nov. 16) 1935.

In a 4 week old infant there developed a tuberous and bullous eruption involving chiefly the face but extending also to the trunk. Shortly after the birth of the child the mother had been given several injections of pernocton (sodium salt of secondary butyl-beta-bromallylbarbiturate). It was concluded that the infant's eruption was a bromoderma due to bromide in the mother's milk.

TECHNIC OF MAKING A DERMATOGRAM AND USE IN TEACHING AND IN CLINIC PRACTICE. W. SCHÖNFELD, Dermat. Wchnschr. **101**:1427 (Nov. 16) 1935.

Schönfeld describes in some detail the method of making a dermatogram. It is the same as that used in taking finger-prints. In teaching, dermatograms are of use in demonstrating variations in the surface architecture of the skin in different areas as well as variations which occur in disease. For practical work the dermatograms show slight changes not visible to the naked eye, such as the early changes in Darier's disease.

THE FERMENT THERAPY OF DERMATITIS HERPETIFORMIS OF DUHRING. J. SELLEI, Dermat. Wchnschr. **101**:1485 (Nov. 23) 1935.

Sellei reports good results from ferment therapy, preparations from the liver and from the pancreas being used, in seven of ten cases of Duhring's disease.

A CASE OF ECTHYMA SIMPLEX STREPTOGENES WITH FATAL OUTCOME. CARL FISCHER, Dermat. Wchnschr. **101**:1513 (Nov. 30) 1935.

Seven years before presenting himself at the clinic, the patient, a 47 year old man, suffered pain and cramps in the right leg. Subsequently whitening and anesthesia developed. The condition cleared up in three weeks, and there had been no further trouble except an occasional mild cramp until two weeks before entry. In attempting to relieve the pain the patient resorted to massage, and a severe ecthyma developed. Death occurred in spite of energetic treatment.

THE DIAGNOSIS OF SYPHILIS FROM A DROP OF DRIED BLOOD BY CHEDIAK'S METHOD. J. WENDLBERGER and K. SCHREINER, Dermat. Wchnschr. **101**:1539 (Dec. 7) 1935.

The authors review the method suggested by Chediak of making a serologic test for syphilis on a drop of dried blood. They report that the results agreed with those of standard methods in 84.7 per cent of 253 tests made. The test is applicable to blood stains on linen or paper.

INVESTIGATION OF THE USEFULNESS OF A SERODIAGNOSTIC TEST WITH DRIED BLOOD SUGGESTED BY CHEDIAK. HERBERT WENDEBORN, Dermat. Wchnschr. **101**: 1543 (Dec. 7) 1935.

Wendeborn compared the result of tests with dried blood with those of the Wassermann and Kahn tests in 575 cases. The method was found to be considerably less sensitive, but the author thinks that it may be of practical use on account of its simplicity.

LUPUS VULGARIS OF THE SCALP. G. TRENK, Dermat. Wchnschr. **101**:1547 (Dec. 7) 1935.

Trenk reports a case of lupus vulgaris of the scalp in a 48 year old hairdresser who had had tuberculosis for over ten years. The present lesion had developed on the site of a burn.

URIC ACID DIATHESIS IN ASSOCIATION WITH CUTANEOUS DISORDERS. WILHELM RICHTER, Dermat. Wchnschr. **101**:1567 (Dec. 14) 1935.

The author describes a case of tophi occurring above the outer malleoli. He discusses the occurrence and clinical characteristics of such swellings.

USE OF PALLIDA ANTIGEN (GAEHTGENS' PALLIDA REACTION) IN CEREBRAL SYPHILIS. GERHARD FRITZSCHE, Dermat. Wchnschr. **101**:1571 (Dec. 14) 1935.

Using a phenolized aqueous suspension of Spirochaeta pallida as an antigen, Fritzsche noted an increased sensitivity of the Wassermann test in cases of cerebral syphilis.

PECULIAR ALLERGY TO LIVER EXTRACT. WILHELM MILBRADT, Dermat. Wchnschr. **101**:1595 (Dec. 21) 1935.

In a 10 year old child who was receiving a liver extract by mouth a dermatitis developed while treatment with acetarsone was administered for congenital syphilis. After several weeks an erythematous eruption developed immediately after each dose of liver extract was taken. The same reaction occurred when other liver preparations were used.

EPIDERMOLYSIS BULLOSA HEREDITARIA DYSTROPHICA LOCALISATA. L. N. MASCHKILLEISSON and L. A. ABRAMOWITSCH, Dermat. Wchnschr. **101**:1600 (Dec. 21) 1935.

The authors describe the case of an 11 year old girl who had a bullous eruption involving principally the trunk from the level of the nipples to the inguinal folds and from the shoulder blades to the sacrum. A few lesions appeared on the scalp and in the mouth. Hypertrophic changes were noted on all the toe-nails and on two finger-nails. The teeth were dystrophic. The limbs showed no lesions even after considerable trauma. The disorder appeared shortly after birth, and the slightest trauma caused a bulla to develop in the affected area. Microscopic examination of sections of material taken from an uninvolved area showed a normal elastic tissue content.

THE RELATIONSHIP BETWEEN BASAL METABOLISM AND SULFUR METABOLISM IN PSORIASIS. SU TZY-CHING, Dermat. Wchnschr. **101**:1624 (Dec. 28) 1935.

In twenty-one cases of psoriasis the author reports a relative decrease in the basal metabolism. The neutral sulfur content of the urine was increased.

GENERALIZED ACUTE ECZEMA DUE TO HYACINTH OIL. ALADÁR VON VARGA, Dermat. Wchnschr. **102**:104 (Jan. 25) 1936.

The author reports that an extensive dermatitis developed after the use of a perfume containing oil of hyacinth, a synthetic product made in the Netherlands. A patch test showed that the patient was sensitive to this product but was not sensitive to alcohol.

TAUSSIG, San Francisco.

HYPERSENSITIVENESS OF GUINEA-PIGS TO ARSPHENAMINE. R. LAUF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:49, 1935.

Guinea-pigs were given repeated intracutaneous injections of small doses (from 0.01 to 0.1 mg.) of neoarsphenamine, and after varying intervals they received intracardiac injections of from 6 to 15 mg. of the same drug. A large number of them reacted with moderate to marked anaphylactic symptoms, but all survived. The results prove that arsphenamine is a full antigen. The optimum interval for the development of hypersensitiveness was six months after the sensitizing injections, and these were more effective when given in repetition. The total quantity of the drug administered for sensitization was not important. The type of food that was given during the winter and the drop in atmospheric pressure favored more intensive anaphylactic symptoms.

LOCAL IMMUNIZATION AGAINST INFECTIONS OF THE SKIN WITH STAPHYLOCOCCI. F. KLOPSTOCK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:213, 1935.

Cutaneous inunctions of staphylococcic vaccines into rabbits were followed after proper intervals by intracutaneous injections of the bacteria, with only slight and irregular evidence of protection. Application of the bacterial suspension in the form of an ointment immediately after the injection of the bacteria into the skin failed to show any influence on the course of the infection.

I. DAVIDSOHN, Chicago. [ARCH PATH.]

A CONTRIBUTION TO THE SUBJECT OF LYMPHOGRANULOMA VENEREUM. COMPLEMENT FIXATION REACTION. S. KINOSHITA and S. KOYAMA. THE WEIL-FELIX REACTION. S. KOYAMA. THE VIRUS CARRIER. T. HASHIMOTO and S. KOYAMA, Jap. J. Dermat. & Urol. **38**:941, 946 and 952 (Dec.) 1935.

These three articles describe results of studies carried on in the dermatologic department of the University of Niigata, Japan. In work on the complement fixation reaction, the pus from bubos and the emulsions of macerated material from enlarged lymph glands obtained by puncture were used as antigens. However, no positive results were obtained, if one excepts a weakly positive reaction in a patient with latent syphilis. The Weil-Felix reaction showed a slight amount of clumping of some strains of Bacillus proteus, but in no instance could the reaction be classed as specific for lymphogranuloma venereum.

In discussing the subject of the method of transference (virus carriers) the case histories of three prostitutes are given. There was no external evidence of the disease, but the purulent discharge from ulcerations of the vagina and rectum and even the clear mucous discharge from the cervix or the serous discharges secured by scratching the walls of the vagina gave a positive Frei reaction when injected intracutaneously into patients with clinical manifestations of lymphogranuloma venereum. In one of the cases there was a history that the woman had infected a male guest in the brothel. The authors believe that when the initial lesion is located deep in the genital tract of women and there is secondary spread toward the rectum and perirectal tissues (esthiomene) the danger of infection is greater because the involvement is not easily detectable and the disease is not treated during the early infectious stage.

INFLUENCE OF ECZEMATOUS CUTANEOUS CHANGES ON RENAL FUNCTION. INFLUENCE ON THE PHLORHIZIN GLYCOSURIA. I. MIYAKE and I. OYAMA. INFLUENCE ON THE DIASTASE CONTENT OF THE URINE. I. MIYAKE and I. OYAMA. INFLUENCE ON THE EXCRETION OF PHENOLSULFONPHTHALEIN. I. MIYAKE and T. HONDA, Jap. J. Dermat. & Urol. **39**:23, 33 and 40 (Jan.) 1936.

In the three articles which are here abstracted it is stated that the dermatitis was induced by croton oil and that rabbits were tested by the customary laboratory procedures. A preliminary control interval (from 3 to 6 tests) established the physiologic norm, then the croton oil was applied, further tests being then repeated after the dermatitis had been present for varying periods of time.

Artificial dermatitis induces abnormal behavior of the phlorhizin glycosuria. In the majority of animals this behavior is consonant with the signs of a lowered renal function, but in a few it indicates rather an accelerated function. The amount of diastases in the urine, on the other hand, is usually increased with the onset of the dermatitis, a gradual decrease during the acute stage, a rise and continued high level during the subacute period and finally a return to normal with the advent of convalescence being noted. In the phenolsulfonphthalein test the induction interval (viz., the period from the time of injection to the instant when the dye appears in the urine), the duration of the excretion and the total amount of dye excreted were all noted, and although the results did not always harmonize, the general trend seemed to indicate a lowering of renal function.

In a few instances a transient albuminuria was noted during the course of the dermatitis.

CHRONIC ANNULAR ERYTHEMA. T. NISHIMAYA and T. SATO, Jap. J. Dermat. & Urol. **39**:314 (March) 1936.

In the four cases of rather typical chronic annular erythema reported by the authors the sella turcica tended to be smaller than normal. In the two female patients, aged respectively 25 and 29, there was irritation of the sympathetic nervous system, and in the two male patients, both of whom were 29 years of age, irritation of the parasympathetic nervous system was present. The two women were sensitive to peptone, the one aged 25 being highly so. According to the author, that patient seemed to have been relieved of the erythemic condition through treatments which brought about desensitization to peptone. The other woman was treated with a nonspecific desensitizing agent.

J. W. BRENNAN, Chicago.

TELANGIECTATIC GRANULOMA AND ITS TREATMENT. KNUT WOLKE, Acta radiol. **17**:117 (April) 1936.

The author discusses at length the literature, the clinical and histologic characteristics and the differential diagnosis of telangiectatic granuloma and granuloma pyogenicum and adds observations in 138 cases of this disease studied from 1921 to 1934 at an institution with which he was associated. The greater number of cases occurred in women, and lesions developed especially during pregnancy, in some instances arising at the sites of preexisting angioma. In only 33 per cent of the cases did the lesions occur at sites of trauma. Trauma is cited as preceding their appearance in from 50 to 75 per cent of cases according to other authors. The pathogenic origin of these lesions is thought to lie between inflammation and tumor, according to Wolke. Puberty, pregnancy and the menopause seem to predispose to the development of the condition in women.

WIEDER, Milwaukee.

Society Transactions

DERMATOLOGICAL CONFERENCE OF THE MISSISSIPPI VALLEY

F. W. Lynch, M.D., *Acting Secretary*

Minneapolis, Sept. 12, 1936

Samuel E. Sweitzer, M.D., *in the Chair.*

A Case for Diagnosis (Tuberculosis Cutis?). Presented by Dr. Samuel E. Sweitzer, Minneapolis, and Dr. Louis H. Winer, Minneapolis.

E. B., a Swedish woman aged 22, first noticed her present eruption in 1931. She states that she had a similar eruption on her arms and feet when she was 7 years old. Since 1931 the lesions have been present on the arms, feet, abdomen and thighs. No treatment was given, and the eruption has not changed appreciably. In October 1935 the patient went to the Mayo Clinic, where a diagnosis of tuberculosis cutis follicularis disseminata was made. Intravenous injections of gold sodium thiosulfate caused the lesions to fade considerably.

Just below the right knee, on the dorsal aspect of both feet, on the abdomen and on the left thigh are groups of small bluish red slightly indurated papules. Under pressure with the diascope the lesions do not completely disappear. On the left thigh are small atrophic scars at the sites of previous lesions.

The Wassermann test of the blood and the Rytz and Kahn tests were negative. Roentgenograms of the chest, skull and stomach showed no abnormalities, and the appearance of the colon, as seen roentgenologically, was interpreted as "irritable bowel." The basal metabolic rate varied from —22 to —7 per cent on repeated determinations. The Mantoux test was negative with a 1:1,000 dilution of tuberculin.

Sections are shown; they reveal an infiltrate in the middle portion of the cutis consisting of epithelioid cells, an occasional giant cell and an irregular surrounding zone of small lymphocytes.

Tuberculosis Cutis (Tuberculid en Plaque). Presented by Dr. Samuel E. Sweitzer, Minneapolis.

M. P., a woman aged 22, was first seen in 1926, when she presented an eruption of eighteen months' duration. She stated that the lesions first appeared on her right ankle and slowly extended until the ankles, legs and wrists were involved. At that time a general physical examination gave negative results. There is no history of tuberculosis in the immediate family, but a maternal uncle died of tuberculosis. In 1926 the Wassermann test and tuberculin tests gave negative results, and a roentgenogram of the chest revealed no evidence of tuberculosis. Treatment consisting of intravenous injections of neoarsphenamine, injections of gold sodium thiosulfate, ultraviolet irradiation and induction of hyperpyrexia was given, but no notable improvement resulted.

In 1930 Professor Gans observed the patient and studied the histologic sections; he suggested the diagnosis of tuberculid en plaque.

In 1934 the patient was thoroughly reexamined, and the Wassermann test gave positive results. During two years in which she received antisyphilitic therapy the old lesions faded and no new ones appeared. Therapy was discontinued during the summer of 1936, and after that the eruption again manifested itself. The lesions at that time were superficial small discrete nodules instead of the circinate plaques which had been present in 1926.

In 1934 the patient was thoroughly studied at the Glen Lake Tuberculosis Sanatorium, and no focus of tuberculosis was found. (Further details on this case are given in: Sweitzer, S. E.: Tuberculide en Plaque, ARCH. DERMAT. & SYPH. **24**:842 [Nov.] 1931.)

In August 1936 the eruption involved the left wrist, both thighs, the portions of both legs near the ankles and both buttocks. The early lesions were superficial bluish red grouped nodules varying from 0.5 to 1 cm. in diameter. In addition soft atrophic scars of healed lesions could be seen. The lesions did not disappear under pressure with the diascope.

The Wassermann and the Kline test both gave a 1 plus reaction in August 1936. The Mantoux test gave negative results with a 1:1,000 dilution of tuberculin; with a 1:100 dilution the results were slightly positive. A roentgenogram of the chest revealed no evidence of tuberculosis.

Biopsies were made in 1926 and in 1935; they revealed nests of epithelioid cells interspaced with giant cells and small lymphocytes. The sections in this case and those in the first case are quite similar.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: In the first case the original diagnosis of tuberculosis cutis follicularis disseminata, which I suggested when the patient was seen at the Mayo Clinic, was made before I had finished studying the histologic classification of tuberculosis. The sections do not show any caseation necrosis but reveal the histologic picture of sarcoid, and this justifies the inclusion of the condition under tuberculosis en plaque. Since this patient was seen at the Mayo Clinic the lesions have undergone a great deal of involution as a result of therapy with a gold preparation.

DR. CLARK W. FINNERUD, Chicago: I noted the marked similarity between the conditions in these two cases, and I think that they should be classed together. Histologically, as well as clinically, I thought it was difficult to classify the condition in the first case under the original diagnosis made by Dr. Montgomery, but I agree with his remarks, and I think that the disease is a mild form of that which is present in the second case.

DR. H. E. MICHELSON, Minneapolis: It seems to me that if these two patients present a type of tuberculosis of the skin may be their condition is the connecting link between granuloma annulare and erythema induratum. One asks himself the question: What are the criteria for the diagnosis of tuberculosis of the skin when the reaction to tuberculin is negative, the search for bacilli reveals none, the general examination gives negative results and the only evidence of tuberculosis is the tuberculoid structure in the microscopic picture? If the morphologic picture corresponds to that of a well known type of tuberculosis that diagnosis is made, and if, as in the first case, it does not, it is difficult to make the diagnosis on the grounds of the histologic picture alone.

DR. H. JERRY LAVENDER, Cincinnati: In the first case I think the possibility of an eruption due to phenolphthalein should be definitely ruled out. The patient admits that until a week ago she was taking ex-lax, phenolax and various compounds of that sort. I think that if she stopped taking these drugs and was subjected to the therapeutic test some definite information might be obtained.

DR. RUBEN NOMLAND, Iowa City, Iowa: I think that a phenolphthalein eruption would not be followed by atrophy, and there is definite atrophy in some of these lesions.

DR. H. JERRY LAVENDER, Cincinnati: I agree that it is unusual to see atrophy in phenolphthalein eruptions, but my co-workers and I have seen it in two patients in Cincinnati. One of the patients, who was presented before the Central States Dermatological Association a few years ago, exhibited marked atrophy, which was demonstrated at the time of the meeting both clinically and histologically. This proved that atrophy does occur in phenolphthalein eruptions if the insult is kept up long enough.

DR. L. H. WINER, Minneapolis: In the second case the clinical findings suggested that the condition was a phenolphthalein eruption. The patient was hospitalized, and any possibility of her getting phenolphthalein was eliminated. There were no changes. She was then given phenolphthalein, and still there were no changes. In the first case when the patient came to the clinic she was questioned about drugs and she stated that she had taken no medication. Because biopsies disclosed the marked similarity in the reaction in these two cases the condition in both was classified in the group of tuberculid en plaque.

NEUROFIBROMATOSIS; SUBEPIDERMAL FIBROSIS. Presented by DR. H. E. MICHELSON, Minneapolis.

Mrs. P. M., aged 35, states that she has had soft and hard nodules on her arms and chest as long as she can remember. No new lesions have developed and those present have not caused any discomfort.

The patient is obese. On the arms and back are small hard nodules ranging from 0.25 to 0.5 cm. in diameter. On the back, beneath the right breast and on the right thigh are soft thin bladder-like formations which can be pressed in a hollow point in the underlying tissue and are not unlike a small ventral hernia. The lesions are similar to those seen in cases of Schweninger-Buzzi's disease.

A CASE FOR DIAGNOSIS (SARCOID?). Presented by DR. JOHN BUTLER, Minneapolis.

This man, aged 73, a German, states that a lesion has been present on his left arm near the elbow since May 1936. A second lesion appeared about a month later near the left wrist; this disappeared almost completely after he received ultraviolet therapy. A third lesion, which is small, has appeared within the past month. There is no family or personal history of tuberculosis or syphilis.

On the extensor surface of the left arm near the elbow is an oval thickened reddish brown plaque measuring 3 by 3.5 cm. A similar lesion 0.3 cm. in diameter is situated near the large one. The skin over the dorsum of the left wrist and that covering the medial surface of the forearm near the elbow is slightly erythematous and feels infiltrated and thicker than normal.

The Kolmer, Wassermann and Kline tests of the blood were negative. The Mantoux test was negative with a 1:1,000 dilution of tuberculin.

Sections are shown; they reveal atrophic epidermis and involvement of the lower portion of the cutis by lobulated masses of epithelioid cells in which a few small lymphocytes are interspersed. These masses are quite dense in the lower and less so in the upper portion of the cutis.

SARCOID (PLAQUE TYPE). Presented by DR. H. E. MICHELSON, Minneapolis.

This woman, aged 41, states that a generalized eruption has been present for a year and a half. Her general health has been good. There is a history of definite exposure to tuberculosis four years ago.

Numerous lesions which are elevated and soft but not tender are present on the trunk. There is no scaling or ulceration. A few hard red nodules of hazelnut size are scattered over the upper portion of the arms, the chest and the back.

Examination of the urine and blood gave negative results.

A biopsy revealed sarcoid.

MILIARY SARCOID. Presented by DR. H. E. MICHELSON, Minneapolis.

This woman, aged 49, states that in 1933 an eruption of hard papules appeared over the arms and persisted for several months. It then completely disappeared, but it reappeared six months later and has persisted, though a few remissions have occurred during treatment. The patient's general health has remained good. She was operated on for gallstones and was treated at the Mayo Clinic for a renal condition which may have been tuberculous.

The Wassermann test gave negative results. Examination of the blood showed 11,050 leukocytes. The differential blood cell count gave the following results: polymorphonuclears, 77 per cent; lymphocytes, 21 per cent; eosinophils, 1 per cent, and monocytes, 1 per cent.

Treatment has consisted of administration of arsenic and ethyl esters of chaulmoogra oil and roentgen therapy.

DISCUSSION

Dr. Clark W. Finnerud, Chicago: The first case in this group interested me considerably because of the marked induration. Histologically the condition seems to be a cross between the superficial and the deep type of sarcoid.

In the last case of the group, were it not for the histologic section, there would be considerable doubt as to the correctness of the diagnosis of miliary lupoid, owing to the lack of color in the lesions; however, the histologic picture definitely confirms that diagnosis.

Dr. H. E. Michelson, Minneapolis: In the past few years there has been a voluminous amount of literature on sarcoid, and the cases presented today demonstrate a great variation in the possibilities in this condition.

Scleredema Adultorum. Presented by Dr. H. E. Michelson, Minneapolis, and Dr. Carl W. Laymon, Minneapolis.

N. H., a boy aged 16, had scarlet fever in January 1936. About Feb. 1, 1936, stiffness of the skin of the neck and back was noted. This process gradually became more diffuse, involving the chest and abdomen to the waist-line, the arms to the elbows and the face. The hands and lower extremities remained normal. Within the past few weeks stiffness of the neck and arms has gradually become less marked. No other member of the family has or had a similar condition.

The skin in the areas mentioned is of putty-like consistency. There are no important surface changes. The movements of the tongue and neck are greatly limited.

Scleredema Adultorum. Presented by Dr. H. E. Michelson, Minneapolis, and Dr. Carl W. Laymon, Minneapolis.

E. J., a school girl aged 14, first noticed stiffness of her neck during the last week of May 1936. This condition gradually involved the cheeks, the arms and the upper portion of the chest, the degree of involvement remaining the same. One week before the onset of the stiffness the patient had a severe attack of pharyngitis associated with fever and general malaise which lasted for four days. The past history is irrelevant except for the fact that frequent attacks of sore throat occurred after a tonsillectomy which was performed in October 1935.

The skin of the face, neck, upper portion of the chest and arms is much firmer than normal. There are no surface abnormalities other than paleness. There is no pitting on pressure, and no changes are noted on the hands and feet. Examination of the urine showed no sugar or albumin. Examination of the blood showed 77 per cent hemoglobin (Sahli) and 8,400 leukocytes. The differential blood cell count gave the following results: polymorphonuclears, 59 per cent; lymphocytes, 35 per cent; monocytes, 5 per cent; eosinophils, 1 per cent. The basal metabolic rate was —4 per cent.

DISCUSSION

Dr. Paul A. O'Leary, Rochester, Minn.: It is interesting to note that the scleredema in these two patients has undergone involution spontaneously. There are two points about this observation which I wish to discuss, (1) the fact that the tendency to such spontaneous recovery must minimize enthusiasm for the various therapeutic agents used in cases of this condition and (2) the fact that spontaneous involution does not always occur, a progression to unfavorable outcome taking place in some cases. A patient who is seen early after the onset of scleredema presents a difficult problem in differential diagnosis because acute

edematous scleroderma, dermatomyositis, diffuse myositis and trichinosis all look much like scleredema adultorum at the onset. Results of histologic study of the skin and muscle during the early phases are not diagnostic, with the exception that in cases of trichinosis the organisms may be demonstrated. Accordingly, it is advisable to make a guarded prognosis until it is possible to establish the diagnosis. I do not mean to say that scleredema adultorum is not an entity; on the contrary, I believe it is a definite syndrome which sometimes progresses to an unfavorable outcome.

DR. CARL W. LAYMON, Minneapolis: My co-workers and I feel that there are sufficient differences between scleredema adultorum and diffuse scleroderma to warrant the consideration of the two conditions as separate entities. Scleredema begins on the nape of the neck, usually after an acute infectious process, and extends down the chest, arms and back, leaving the hands free. Diffuse scleroderma as a rule begins on the hands and extends up the arms. The histologic changes in the two cases of scleredema which we studied consisted chiefly in edema of the cutis.

DR. THEODORE CORNBLEET, Chicago: My co-workers and I have studied the calcium metabolism in cases of this condition for some time, and we have found that there is a definite calcium retention in cases of scleroderma. We believe that scleroderma belongs to a definite group, as stated by Dr. O'Leary. There is probably a toxin that injures the tissue, and, conceivably, as a result of this insult, there is a deposition of calcium. The calcium content of the urine in cases of scleroderma is low, but by proper measures it can be sufficiently increased to prevent retention of calcium in the body. The nonatrophic tissues may then return to normal. I think that in many cases the tissues pick up calcium. If the calcium can be removed there is a tendency for the lesions to regress.

MALIGNANT MELANOMA. Presented by DR. S. E. SWEITZER, Minneapolis, and DR. CARL W. LAYMON, Minneapolis.

M. M., a French woman aged 70, states that she first noticed a black spot on her right heel when she was 30 years old. It became eroded and enlarged during the summer of 1935. She noticed "lumps" in the right inguinal region in October 1935 and observed a lesion similar to that on the foot near the left elbow in January 1936. Her weight one year ago was 140 pounds (63.5 Kg.), and at present it is 122 pounds (55.3 Kg.).

There is an ulcerated nonpigmented granulating neoplasm on the right heel which measures 1 cm. in diameter. An extremely firm node, measuring 7 cm. in diameter, is present in the right inguinal region, and there is a node 1 cm. in diameter in the left epitrochlear region. At the time of the last examination the liver was not enlarged and there were no cutaneous metastases.

In January 1936 a biopsy of material from the right inguinal node showed malignant melanoma.

MALIGNANT MELANOMA. Presented by DR. H. E. MICHELSON, Minneapolis.

This Swedish man, aged 72, came to the University Hospitals in August 1935, complaining of a growth of two years' duration on the right cheek. His physician told him that the lesion was a wart and excised it in the fall of 1934. When the patient was first seen at the University Hospitals there was a hard nodular scar on the right cheek at the site of the operation, and palpable cervical nodes were present on the right side. Biopsy of material from the lesion on the cheek showed malignant melanoma.

The patient's condition apparently did not progress until August 1936, when numerous nodules of various sizes appeared on the chest and back. His weight has decreased from 150 to 132 pounds (68 to 59.9 Kg.) since May 1936.

There is a firm reddish blue subcutaneous tumor measuring 2 cm. in diameter on the right upper portion of the abdomen near the costal margin. Several smaller pigmented and nonpigmented nodules are present on the back. The liver is not enlarged.

DISCUSSION

Dr. S. W. Becker, Chicago: I think there is no doubt about the diagnosis. In the first case the section shows typical nonpigmented melanoma. The interesting feature is that the patient first noticed a lesion, which she claims was black but which a relative said was brownish, on her heel when she was 30 years old. In all probability this lesion belonged in the class of lentigo or lentigo maligna. It is noteworthy that forty years elapsed before the patient noticed a change in the lesion and a characteristic metastatic glandular swelling developed in the groin. If the lesion was black in the beginning, as the patient states, it probably has been malignant for forty years. On the sole it is unusual for pigment which would produce this dark color to be deposited in the chromatophores. I think that melanomas metastasize much later than the various textbooks state. Treatment is only palliative at this stage, and the condition is hopeless.

Dr. H. E. Michelson, Minneapolis: My co-workers and I think it is important to remove moles occurring about the finger-nails, toe-nails or soles, and we believe that this should be done regardless of the color of the lesion. I do not believe that a careful study and review of the literature will show that the proper removal of a mole ever made it malignant, and I think that it is impossible to state on the basis of their color which moles are dangerous. Certainly, many so-called slate-blue moles are highly malignant, but conversely many highly malignant moles are not slate blue.

Dr. Oliver S. Ormsby, Chicago: In a consideration of the development of a secondary malignant growth in these cases it is necessary to remember that the time element varies a great deal. I recently saw a woman aged 28 who had a large tumor mass on one side of the neck beneath the ear. According to the history a small black spot appeared on the helix of the ear one and a half years previously. This was removed by electrolysis. Six months later nodules developed back of the ear, and about four or five months after the appearance of the nodules the tumor mass in the neck appeared. In the majority of cases of malignant melanoma which I have observed the patients were young rather than elderly, and in most of the cases the malignant degeneration followed surgical removal or irritation. These facts raise an important question as to the advisability of surgical intervention or other treatment. If the lesion is in a location where there is no possible danger of irritation the chances are good that it will remain harmless if it is left alone. I have observed cases in which apparently benign melanomas were completely and thoroughly removed by surgical procedure and in which a general dissemination occurred within a few months. The lesion that gives one the greatest concern is the bluish black or black mole situated on the extremities or around the eye. The ordinary brown mole rarely undergoes malignant transformation, though it may do so.

Dr. Hamilton Montgomery, Rochester, Minn.: There is a wide variation in the time element as regards the development of metastases from melanoma, and I know of one patient who lived for twenty years after metastasis had occurred. Dr. Farrell in an analysis of two hundred and sixty-five cases of melanoma studied at the Mayo Clinic found it difficult to evaluate accurately the result of surgical removal as compared with that of roentgen therapy. One is inclined to criticize the surgeon for not excising tissue widely enough around a melanoma, but it has been my experience that in many cases histologic studies reveal that the lymph and blood vessels in the cutis are packed with tumor cells at the time the melanoma is removed. Obviously in those cases the process has already disseminated, metastasis being often to minute foci which are not apparent in the skin and no clinical sign of extension up the lymphatics being present. In those cases any local therapy is obviously doomed to failure. I agree that the ordinary brown pigmented nevi are usually harmless even when they occur on exposed surfaces.

MYCOSIS FUNGOIDES. Presented by DR. H. E. MICHELSON, Minneapolis, and DR. SAMUEL E. SWEITZER, Minneapolis.

A. C., a farmer aged 63, states that he first noticed nodules on his skin in June 1934. They were located on the trunk and extremities, were moderately pruritic and gradually increased in number. In March 1935 roentgen therapy was given to the lesions, and they completely disappeared. During the past few months a few new plaques have developed. The patient's weight has remained stationary.

On the arms, buttocks and legs are several erythematous plaques varying in size from that of a 10 cent piece to that of a dollar. Some are pigmented; others are erythematous and show slight scaling and induration. Large plaques of pigmented, lichenified dermatitis associated with varices are present on both legs. There are no palpable lymph nodes.

A roentgenogram of the chest revealed a Ghon tubercle and calcified mediastinal glands. Examination of the blood showed 7,900 leukocytes. The differential blood cell count gave normal results.

MYCOSIS FUNGOIDES. Presented by DR. H. E. MICHELSON, Minneapolis, and DR. JOHN F. MADDEN, St. Paul.

E. G., a Swedish woman aged 36, states that she underwent a splenectomy in 1930 because of anemia and leukopenia. The spleen weighed 1,300 Gm. and showed periarterial fibrosis, engorgement of the sinuses and hypertrophy of the pulp. The diagnosis was splenic anemia. In June 1931 enlargement of the liver, generalized pruritus and bleeding from the rectum occurred. An eruption which "looked like ringworm" appeared on the legs and persisted for several years. During the past year nodules have appeared on the legs; some of these have enlarged, forming ulcerating tumors.

On the patient's face, arms and trunk are numerous erythematous slightly scaly oval and circular indurated plaques with sharply demarcated borders. On the legs and thighs in addition to the plaques there are many large elevated tomato-like tumors measuring from 4 to 5 cm. in diameter. Some of these lesions are ulcerated and covered with brownish red crusts. The cervical and axillary lymph nodes are hard, shotty and bean-sized.

In 1930 the blood cell count showed 2,100 leukocytes and the hemoglobin content was 35 per cent. The results of the differential blood cell count were as follows: polymorphonuclears, 46 per cent; lymphocytes, 50 per cent; monocytes, 4 per cent. In 1931 there were 8,500 leukocytes and the hemoglobin content was 60 per cent. In 1936 there were from 11,000 to 24,000 leukocytes and the hemoglobin content was 80 per cent. The results of the differential cell count were normal, except for the fact that the percentage of monocytes was 14 on one occasion. The neutrophils showed a shift to the left, suggesting a severe infection.

Biopsy of material from a lymph node showed reticular hyperplasia. Diagnoses were suggested by three pathologists, two favoring the diagnosis of Hodgkin's disease and one that of inflammatory hyperplasia.

Sections from plaques and tumors are presented.

DISCUSSION

DR. PAUL A. O'LEARY, Rochester, Minn.: It might be well to record the experience which my co-workers and I had in the treatment of mycosis fungoides with derivatives of chaulmoogra oil. As often happens, in the first few cases the results were encouraging, but time and the results in a larger series of cases have cooled our enthusiasm. We have treated seven patients with mycosis fungoides; some were given chaulmoogra oil alone; others took derivatives of chaulmoogra oil and received fever therapy, and the results were insignificant. In a few of the cases the pruritus was decreased somewhat and perhaps the new lesions were slower in developing. We have tried the product used by Lomholt as well as a domestic preparation, and the results have been similar.

LEUKEMIA CUTIS. Presented by DR. C. D. FREEMAN, St. Paul, and DR. F. W. LYNCH, St. Paul.

W. F., a man aged 55, noticed a nodule near the left eyebrow seven years ago. This lesion disappeared spontaneously several years later, and a larger mass appeared on the left arm and remained for a year or more. A generalized nodular eruption has appeared in the last two or three years. A few of the lesions have undergone spontaneous involution, and many have been treated with unfiltered roentgen radiation, usually responding to doses of from 300 to 600 roentgens. In the last few months the lesions have become pruritic.

The patient has also suffered from swelling and stiffness of the joints; the bones are tender to pressure. His general health has been good except for the fact that there is a slight anemia, and the patient complains of some loss of strength. He has lost 15 pounds (6.8 Kg.) during the past eighteen months in spite of general supportive measures. A syphilitic infection acquired thirty years ago was treated early and persistently. A series of injections of a bismuth preparation had no effect on the present eruption. Mapharsen also was given, and as a result of that medication new lesions did not appear so rapidly for several months. A similar effect was obtained with solution of potassium arsenite.

The patient's brother, with whom he has lived, has been hospitalized several times for pulmonary tuberculosis.

Hundreds of nodules are scattered over the entire body; some are small, firm and situated in the subcutis, but the majority are elevated and moderately firm. A few larger and darker plaques measuring 4 or 5 cm. in diameter are present. The greatest number of lesions are situated on the buttocks, arms and legs.

The results of the Kolmer test were negative; the Kline test gave a 4+ reaction. A roentgenogram of the chest showed no abnormalities. The results of the Mantoux test were negative with 1:10,000 and 1:100 dilutions of tuberculin. The blood cell count, made by Dr. Downey, showed from 7,500 to 9,500 leukocytes. The differential blood cell count gave the following results: polymorphonuclears, 75 per cent; lymphocytes, 21 per cent; eosinophils, 4 per cent; basophils, 1 per cent. A report made in January 1935 stated: There are small dark cells, not lymphocytes, which may be tumor cells. Some large lymphoid cells which are present may also be tumor cells. The condition does not seem to be leukemic reticulo-endotheliosis. On November 1935 it was reported that occasional slightly toxic polymorphonuclears were present but no evidence of leukemia was observed. In June 1936 there was no evidence of leukemia; some polymorphonuclears were recognized as toxic, and some showed hypersegmentation of the nucleus. A few medium-sized lymphocytes had peculiar grooved nuclei.

Sections are shown. They reveal large circumscribed masses of small lymphocytes with a few plasma cells, and in some places there are masses consisting almost entirely of plasma cells. Both the cutis and the subcutis are involved.

DISCUSSION

DR. C. D. FREEMAN, St. Paul: There probably should be a question mark after the diagnosis, but clinically the cutaneous manifestations resemble leukemia cutis more than anything else. One must remember that the process has been going on for seven years, and, as yet, no changes in the blood have occurred. If they are going to manifest themselves, it is almost time. We were unable to make a definite diagnosis. The patient had syphilis thirty years ago and was recently treated for it, but no change in the present cutaneous manifestations resulted from that treatment. The condition is gradually becoming worse in spite of all efforts.

DR. OLIVER S. ORMSBY, Chicago: I think this is an extraordinarily interesting case, and I believe that the diagnosis fits as well as any that could be presented. Lymphosarcoma is to be considered, but I have never observed a case of lymphosarcoma in which the lesions were as soft as those exhibited by this patient. In the cases I have observed there were definite nodules or tumors which soon metastasized to the glands, and it was not long before death occurred. On the

other hand, I have never seen an aleukemic blood picture in a case of nodular leukemia of the skin. In cases of erythroderma in which the blood picture was normal I have in several instances made a diagnosis of leukemia, and in those cases the true leukemic blood picture has developed within from one to three years. I believe that this case is one of leukemia cutis.

DR. H. RATTNER, Chicago: In a case of the nodular type of leukemia cutis which I observed for five years in Dr. Pusey's practice the blood picture has remained normal.

DR. C. D. FREEMAN, St. Paul: It has been suggested that leprosy be taken into consideration in this case. The ulnar nerve is not palpable, and there are no changes in the eyebrows and no anesthesia. The patient has no rhinitis or laryngitis.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: The histologic picture is definitely that of lymphoblastoma, resembling most closely that of lymphatic leukemia. There are not enough mitotic figures to suggest lymphosarcoma. Monocytic leukemia should be ruled out by more careful study. It is not unusual for lymphatic leukemia to remain confined to the skin, the blood remaining normal for several years, but in this case the process has remained confined to the skin for an unusually long time.

DR. F. W. LYNCH, St. Paul: I think the results of the first blood smear should be mentioned. The blood was examined by Dr. Downey, who observed rather numerous cells which he was unable to recognize. They were not endothelial cells but probably were some type of tumor cell. Since then such cells have not been observed. Another thing is that in the histologic picture in addition to the lymphocytic infiltrate there are large numbers of plasma cells, namely, real masses of plasma cells separated from the lymphocytes by only a few strands of connective tissue.

PEMPHIGUS VULGARIS. Presented by DR. SAMUEL E. SWEITZER, Minneapolis, and DR. H. E. MICHELSON, Minneapolis.

D. E., a Scandinavian man aged 65, states that he first noticed redness and "watering" of the eyes in 1929. His vision was previously good, but it gradually decreased until he became almost entirely blind in 1932. Blisters appeared in the mouth in 1931, and the oral cavity has been sore ever since, never healing completely. Weeping raw areas appeared in the axillae in 1933. These lesions have practically healed at various intervals but have broken down again.

In April 1934 the margins of the eyelids were edematous and there were cataract and symblepharon in both eyes. Multiple erosions (ruptured bullae) were present on the roof of the mouth and on the buccal mucosa. In the axillae were oozing denuded reddened areas which suggested multiple ruptured coalescent bullae. No lesions were noted elsewhere.

The patient has been under observation since April 1934, and the condition has remained about stationary. The general health has been good, and the weight has increased 30 pounds (13.6 Kg.) during the past two years.

Treatment has consisted of administration of viosterol and tryparasamide and of various soothing local applications.

Sections are shown. They reveal large epidermal bullae with slight cellular infiltrate and dilated blood and lymph vessels in the upper portion of the cutis.

PEMPHIGUS FOLIACEUS. Presented by DR. H. E. MICHELSON, Minneapolis, and DR. F. W. LYNCH, St. Paul.

L. D., a man of Welsh and English descent aged 55, states that he first noted pruritic, burning grouped vesicles over the scapulae in March 1928. During the following months the eruption extended to the arms and legs. It appeared intermittently during the following two years. The patient was presented before the Section on Dermatology at the meeting of the American Medical Association in 1929, and the majority of members present agreed on a diagnosis of dermatitis

herpetiformis. During June and July 1930 he received six intravenous injections of neoarsphenamine without any apparent reaction. While the patient was living in Florida in the autumn of 1930 the eruption became quite generalized and assumed a bullous character. In the spring of 1931 exfoliation began and rapidly became generalized. No bullae have ever developed in the mouth. Since 1931 the patient has received various treatments at numerous institutions, but no significant improvement has occurred.

While he was at the University Hospitals a slight improvement was noted, the most pronounced change occurring during a course of fever therapy. Hyperpyrexia has been induced with malaria and typhoid vaccines and with the Kettering hypertherm. Quinine sulfate and chromium sulfate have been given orally. Recently a series of injections of germanin (from 0.3 to 1 Gm.) have been given.

There is a generalized erythematous scaly and crusted eruption. The palms and soles are slightly thickened and hyperkeratotic. No lesions are present on the mucous membranes. From time to time bullae have appeared in groups. The lesions are easily ruptured, and when they are opened a denuded surface remains.

Numerous examinations of the blood and urine have given negative results. Blood examined by Dr. Welsh, of the Mayo Clinic, in February 1936 gave a positive reaction for the pemphigus antigen and negative reactions for the antigens of erythema multiforme and dermatitis herpetiformis.

NOTE.—The patient died in December 1936, severe anemia and terminal bronchopneumonia having developed. Postmortem examination disclosed no significant changes.

DISCUSSION

DR. OLIVER S. ORMSBY, Chicago: The point of interest about the first case is the involvement of the cornea. For several years oculists have presented patients with lesions on the cornea without any cutaneous manifestations. When there are lesions on the skin as well as on the cornea the diagnosis of pemphigus is clear. Whether true pemphigus, as that disease is known, can develop on the cornea and remain limited to that region is doubtful, I think.

DR. RUBEN NOMLAND, Iowa City, Iowa: Within the past week Dr. Allen has called to my attention two cases of pemphigus of the eye associated with oral lesions of four and six years' duration, respectively. In both the manifestations were essentially the same; there were growing together of the lids and almost complete blindness from opacities in the cornea, as in this case. Most interesting of all was the fact that there were lesions of the mucous membrane without cutaneous involvement. There were lesions of the mouth and vagina, and in one case the visible mucosa of the anus was involved. The oral lesions were painful eroded red areas, not unlike those seen in cases of cutaneous pemphigus with oral lesions. The long duration of the lesions in the eye and mouth in cases of ocular pemphigus seems to put that condition in a category different from pemphigus of the skin with oral lesions. It is the experience of most dermatologists that cases of pemphigus in which oral lesions are present usually terminate fatally in a relatively short time. I do not believe that ocular pemphigus changes to ordinary cutaneous pemphigus except rarely. On the other hand, I observed a case of cutaneous pemphigus with oral lesions in which ocular lesions developed and death occurred within six months; this indicated that the eye can be involved in cases of ordinary pemphigus. Apparently there are more differences than similarities between ocular pemphigus with oral lesions and ordinary pemphigus with oral lesions, and the two conditions probably are entirely different entities.

DR. H. E. MICHELSON, Minneapolis: Pemphigus of the eyeball is chronic and eventually produces complete blindness.

DR. NORMAN TOBIAS, St. Louis: I was interested in hearing that the second patient had been treated with germanin. This drug is a carbamide of a complex salt of trisulfonic acid.

The drug was originally introduced by Klein in 1921 in the treatment of trypanosomiasis, in which it has been remarkably successful. Homann and others have used it in treating multiple sclerosis, obtaining varying results. Veiel in 1931

first suggested its use in treatment of pemphigus. He reported three cures among four patients and requested that further experimentation with the drug be carried out.

As a rule the injections are well borne, although occasionally a chill or a rise in temperature does occur. The urine must be examined after each injection. The presence of a moderate amount of albumin or of a few casts in the urine or an increase in the nonprotein nitrogen content of the blood necessitates a reduction in the dosage, a lengthening of the interval between injections and careful observation of the patient. Tests of the renal function must be carried out after the course of injections is completed.

Regarding the nature of the action of germanin in pemphigus the following theories may be advanced: (1) any change in therapy often produces a remission; (2) the drug may act on the specific cause of the disease; (3) the improvement may be due to changes in the plasma or to cellular changes since the drug has an effect on the coagulability of the blood.

DR. S. W. BECKER, Chicago: My co-workers and I saw a patient with pemphigus who after being treated with germanin suffered from complete atrophy of the adrenal glands, possibly as a result of toxic action of the drug.

DR. CHESTER A. DOTY, Detroit: Recently my associates and I attempted to use germanin in treatment of pemphigus. Our experience with the drug has not been satisfactory.

NECROBIOSIS LIPOIDICA DIABETICORUM. Presented by DR. SAMUEL E. SWEITZER, Minneapolis, and DR. CARL W. LAYMON, Minneapolis.

L. A., a school girl aged 17, first noted an erythematous plaque on her right leg two years ago. No history of trauma preceding the eruption could be elicited. The lesion increased slowly in size during the following eighteen months, and a second plaque developed above the first about one year ago. In April 1936 the patient received a blow over the larger lesion, and ulceration followed. The patient is known to have diabetes; dietary regulation and administration of insulin have been necessary in the past six years. Since the appearance of the ulceration, treatment has consisted of dressings of zinc oxide ointment. The sugar content of the blood has been kept at a normal level by the daily administration of 55 units of protamine insulin.

On the anterior surface of the right leg are two oval plaques with sharply demarcated borders. The margins of the lesions are elevated and bluish red; the central portions are yellowish orange. Numerous telangiectatic vessels are present over the yellow areas. The center of the larger plaque, the site of previous ulceration, is composed of smooth slightly erythematous scar tissue.

The cholesterol content of the blood was 190 mg. per hundred cubic centimeters. The sugar content of the blood and that of the urine were within normal limits at the last examination.

Sections are shown; they reveal heavy collections of lymphocytes mostly about the blood vessels in the cutis. Sections stained with sudan III showed tiny droplets of lipoid within the masses.

NECROBIOSIS LIPOIDICA DIABETICORUM. Presented by DR. SAMUEL E. SWEITZER, Minneapolis, and DR. CARL W. LAYMON, Minneapolis.

A. L., a Swedish girl aged 14, first noticed red spots on her legs during the summer of 1935. The lesions have not changed appreciably since they appeared. The patient has had diabetes for nine years, the condition being controlled by dietary restrictions and administration of insulin. The patient states that she fell down a flight of stairs and injured her legs just before the lesions appeared.

On the anterior aspect of the left tibial surface midway between the ankle and the knee are two erythematous roughly oval plaques. There is no scaling, ulceration or crusting. A smaller though similar lesion is present on the left tibial surface. The waxy appearance and telangiectatic vessels frequently observed in cases of necrobiosis lipoidica diabeticorum are not visible.

Under the diabetic management which the patient is following the sugar content of the urine and that of the blood have remained normal.

Sections are shown. The histologic changes are similar to those described in the first case.

NECROBIOSIS LIPOIDICA DIABETICORUM. Presented by DR. H. E. MICHELSON, Minneapolis.

K. D., a girl aged 12 years, has had diabetes for seven years; administration of insulin and dietary restrictions are necessary. In 1931 a lesion, at first thought to be a bruise, appeared on the right ankle. About eight months later a similar lesion was noted on the right calf. New lesions have developed during the past months, according to a communication from the patient's mother.

When the patient was seen in 1934 there were four erythematous plaques on the lower extremities. The case was reported in full in *The Journal of the American Medical Association*. (Michelson, H. E., and Laymon, Carl W.: Necrobiosis Lipoidica Diabeticorum, *J. A. M. A.* **103**:163 [July 21] 1934).

NECROBIOSIS LIPOIDICA DIABETICORUM. Presented by DR. H. E. MICHELSON, Minneapolis, and DR. CARL W. LAYMON, Minneapolis.

J. M., a woman aged 24, has had diabetes for several years.

This case will be reported in the ARCHIVES (Michelson, H. E., and Laymon, C. W.: Necrobiosis Lipoidica Diabeticorum [Case 3]).

DISCUSSION

DR. E. P. ZEISLER, Chicago: At the meeting of the American Dermatological Association in Boston a group of cases were presented in which the clinical phenomena were almost identical with those observed in these cases. The thing I consider particularly instructive about this disease is that it was apparently overlooked for many years. It was probably diagnosed as scleroderma, erythema induratum and various other things.

DR. MARCUS R. CARO, Chicago: This disorder apparently is not confined to Boston, Chicago or Minneapolis.

DR. CLARK W. FINNERUD, Chicago: In the group of cases presented recently in Boston some of the lesions, as in one case presented today, showed clinically an infiltration with no evident atrophy and no yellowish color, thus leaving some question as to whether the condition was the same as in the other cases. As histologic sections were not presented with the cases at the meeting in Boston some members questioned whether those cases were examples of necrobiosis lipoidica diabeticorum. In one of the cases in this group in which the most important clinical manifestations are lacking the histologic section definitely shows the same picture as does the section in the case in which the clinical manifestations are present.

DR. CARL W. LAYMON, Minneapolis: In all our cases trauma of some type preceded the development of the lesions of necrobiosis. All traumatic lesions in diabetic patients, however, do not assume the characteristics of the lesions of this condition.

The lesions in necrobiosis are more typical clinically than histologically, and similar histologic changes may at times be found around ulcers of the legs, boils and carbuncles in nondiabetic patients.

ORAL THRUSH. Presented by DR. H. E. MICHELSON, Minneapolis.

This boy, aged 6 years, has had the condition for some time. The tongue and mucous membrane of the cheeks are heavily coated with a fungous growth.

Thrush fungi were demonstrated microscopically.

DISCUSSION

DR. E. P. ZEISLER, Chicago: I wish to ask Dr. Michelson what therapy he has used or intends to use. My co-workers and I find this condition resistant

to treatment. I think there are two varieties of thrush: a superficial type which occurs in young children and readily disappears when treated locally with antiseptics and a more severe type with deeper involvement which might be termed submucous thrush and is resistant to treatment.

DR. H. E. MICHELSON, Minneapolis: The best results I have had in the treatment of oral thrush have been with the use of a weak solution of trichloro-acetic acid. The age of the patient also makes a difference, and in some cases the lesions have disappeared when the patient reached adolescence.

DR. THEODORE CORNBLEET, Chicago: I have under observation a man with a long-standing case of oral thrush who in addition to oral lesions has involvement of every finger-nail. He has a large amount of the sugar-like reducing substance in the saliva. I have tried to bring about a reduction in the sugar content of his blood, but this does not help his clinical condition or influence the salivary reducing substance much. Fair results have been obtained with roentgen therapy to the paronychia and treatment with radium to the oral lesions.

KERATOSIS FOLLICULARIS (DARIER). Presented by DR. SAMUEL E. SWEITZER, Minneapolis, and DR. L. H. WINER, Minneapolis.

Mr. J. D., aged 74, who is Scotch-Irish, states that his eruption is of twenty-eight years' duration. It began on the face and gradually involved almost the entire body. He has been given many types of treatment without benefit. There is no history of ingestion of arsenic. His paternal grandfather, his father, one son, two daughters and two male grandchildren are said to have a similar eruption.

The patient is well developed and is apparently in good health. The scalp, the face, the sides of the neck, the lower central portion of the back and the groins are involved in the eruption. The chest, the upper portion of the back, the abdomen and the lower extremities are free from lesions. No lesions are visible on the mucous membranes. The palms and soles are studded with round punctate keratotic lesions. The nails of both hands and to a less extent those of the feet are dry, rough, extremely friable and traversed by numerous longitudinal ridges and furrows. The cutaneous lesions are keratotic brownish red follicular papules which coalesce in the areas mentioned to form crusted vegetating plaques.

The Wassermann, Rytz and Kahn tests on the blood gave negative results.

Sections are shown. They reveal hyperkeratosis and acanthosis of the epidermis. Grain cells and corps ronds are present.

KERATOSIS FOLLICULARIS (DARIER). Presented by DR. SAMUEL E. SWEITZER, Minneapolis, and DR. ELMER M. RUSTEN, Minneapolis.

Mr. J. G., aged 32, states that his eruption has been present since 1921. It began at the waist-line and remained there for ten years. In 1931 the patient fractured some vertebrae and was placed in a plaster cast which covered the trunk. When the cast was removed the lesions appeared on the face, chest, abdomen and back. The family history is irrelevant.

The eruption is present on the face, shoulders, flanks, groin and back. In these areas the skin is covered with multiple keratotic reddish brown follicular papules. Palpation of the affected portions suggests a nutmeg grater feel. Most of the lesions are discrete, but in a few areas they are closely grouped. No crusts or scales are present, and the mucous membranes are not involved. The skin of the palms is yellowish and hyperkeratotic. No lesions are present on the lower extremities.

The Kahn and the Rytz test of the blood gave negative results.

Sections are shown. The histologic picture is the same as in the first case.

KERATOSIS FOLLICULARIS (DARIER). Presented by DR. H. E. MICHELSON, Minneapolis.

T. J., a woman aged 20, first noticed pruritic crusted papules on her neck and scalp in the spring of 1929. Similar lesions developed rapidly on the forehead,

behind the ears and in the axillae and groin. About in September the lesions usually improved considerably, and the patient suffered no discomfort during the winter, but she had an acute exacerbation of the eruption every spring; this gave her so much discomfort that she was unable to continue her employment as a maid. Her maternal grandmother, her mother and three sisters have a similar condition. Five brothers have no eruption. The patient has used various types of local applications, obtaining only transient relief.

The scalp, forehead, postauricular region, axillae and groin are involved. The essential lesions are discrete keratotic yellowish brown papules. Many of them have become confluent and are covered with a greasy tenacious scale. A few pustules have been found in the axillae and on the external genitalia.

The Wassermann, Kahn and Kline tests of the blood gave negative results.

KERATOSIS FOLLICULARIS (DARIER). Presented by DR. H. E. MICHELSON, Minneapolis.

J. C., a woman aged 21, states that when she was 7 years old keratotic lesions were observed on her palms. Three years later a papular eruption appeared on her face and neck. The eruption continued to extend, and the lesions became darker after she was given roentgen therapy at another clinic. When the patient was aged 15, lesions similar to those on the hands appeared on the feet. As far as is known arsenic has not been administered. The eruption has remained stationary for several years.

There is an extensive papular eruption involving the face, the neck, the chest and the distal portions of all the extremities. The lesions are dark brown sharply circumscribed papules; the underlying skin is yellowish brown and presents an oily appearance. The eruption is most severe in the region of the nose, chin and ears. The entire surface of the palms and soles exhibits a thickened, keratotic appearance. The remnants of a moderately severe acne of the face are also observed.

DISCUSSION

DR. F. E. SENEAR, Chicago: This group of cases brings up a question. About a year ago my co-workers and I observed in the hospital a woman from the southern portion of the state who had some lesions which we thought were keratosis follicularis, but there were some lesions of dermatitis vegetans in the flexures. She had had this condition for many years and said that it cleared up during the summer and became much worse in the winter. About a month ago her son presented himself; he had typical keratosis follicularis. A request for his admission had been made because an acute outbreak was anticipated. His condition too was much worse in the winter. One of the patients presented today said that there is marked improvement in the winter and that the condition is worse in the summer. Another patient said there is not much change. I have never seen a patient with keratosis follicularis whose lesions disappeared completely during the summer.

DR. CLARK W. FINNERUD, Chicago: I think that, as in cases of lupus erythematosus, in cases of keratosis follicularis lesions of the mucous membrane of the hard and soft palate and sometimes lesions of the conjunctiva are much more common than is usually believed, because these areas are not usually examined. I noticed that the man with the markedly disseminated eruption had some lesions in the mouth.

DR. PAUL A. O'LEARY, Rochester, Minn.: I can confirm what Dr. Senear has said about this condition undergoing involution temporarily. My colleagues and I recently had a patient who had exacerbations during the summer and was entirely free from the keratoses during the winter. He had completed his studies for the ministry, but when he appeared before the board for his final examination during the summer the board refused to admit him because the keratosis follicularis was so severe. He had "gotten by" in the previous years because the lesions had not reappeared to any great extent during the school year.

NAEVUS PIGMENTOSUS RESEMBLING XANTHOMA. Presented by DR. H. E. MICHELSON, Minneapolis, and DR. F. W. LYNCH, St. Paul.

This girl, aged 18 months, has had a lesion on the abdomen since the age of 2 months. Her mother states that some other lesions then appeared and gradually increased in size until the patient was 1 year old. During the past few months the lesions have become flatter.

On the face, neck, abdomen and legs are multiple soft, yellowish brown new growths varying from 0.5 to 1 cm. in diameter.

A roentgenogram of the skull showed no abnormalities.

The Wassermann and the Kahn test of the blood gave negative results.

Sections stained for fat are shown.

DISCUSSION

DR. F. E. SENEAR, Chicago: This is an interesting case. When I first saw the patient I thought of urticaria pigmentosa and of nevoxantho-endothelioma or the ordinary juvenile type of xanthoma. I then noticed the diagnosis of naevus pigmentosus. If the condition is the juvenile form of xanthoma, the lesions are not at all like those in the case which Dr. Caro and I reported (ARCH. DERMAT. & SYPH. **34**:195 [Aug.] 1936), for in that case the lesions were bright yellow and sharply circumscribed and projected from the skin, whereas in this case the lesions look much like those in other reported cases of nevoxantho-endothelioma. The sections stained for fat and the histologic picture in general, however, do not support that diagnosis. Closer observation shows that the lesions definitely urticate when they are scratched. The mother states that she has noticed this also. It is my opinion that the condition is probably urticaria pigmentosa with an atypical histologic picture.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I thought the histologic picture was that of a nonpigmented type of naevus pigmentosus. I could see no mast cells.

DR. OLIVER S. ORMSBY, Chicago: I believe that this patient has urticaria pigmentosa. If the lesions are pigmented nevi, the dermatographia can be accounted for only on the ground that the patient's entire skin undergoes urtication when it is scratched. As I scratched a lesion it definitely became edematous and erythematous but the redness extended to the region immediately surrounding it, the edema being limited to the lesion. I think that the condition is urticaria pigmentosa with xanthoma-like lesions.

DR. CLARK W. FINNERUD, Chicago: I think that urticaria pigmentosa is probably rightly classed as a form of nevus. About fifteen years ago I reviewed the literature on urticaria pigmentosa and reported a case in which there were macular and nodular lesions and in which the infiltrate was composed of cells that were almost solely cuboidal, as in this case, instead of being the fusiform or elongated type of mast cell. With the Pappenheim-Unna pyronine and methylene green stain the granules were much more clearly demonstrated than with Unna's polychrome methylene blue. A similar instance was observed at the Central Free Dispensary of the Rush Medical College. I am sure that Dr. Nomland recalls the histologic observations in both of these cases and will agree that the condition was urticaria pigmentosa. In urticaria pigmentosa, histologically, one commonly sees the cells in nests and columns, just as in nevi, and not infrequently the mast cells are cuboidal as in the sections shown. I feel certain, because of both the clinical and the histologic picture that the condition in this case should be classed as urticaria pigmentosa.

DR. S. W. BECKER, Chicago: If the lesions are nevi they present an unusual microscopic picture. Sections from deep down in pigmented nevi show the elongated nerve type cells. In this case all the cells, superficial and deep, are of the same type, and while there are no basophilic granules, such as are usually seen, and no mast cells, the entire cellular protoplasm does take the bluish stain. I agree with Dr. Finnerud that the condition is urticaria pigmentosa.

DR. F. W. LYNCH, St. Paul: This case was presented because of the clinical resemblance of the nevoid manifestation to naevoxantho-endothelioma. When the patient was first seen the lesions were more elevated and more yellow; today they are smoother and darker. This cycle is also observed in the aforementioned disease. If a histologic study had not been made the case would have been regarded as an example of naevoxantho-endothelioma. The pale cells seen in the sections have been regarded not as typical mole cells but rather as a degenerative phase of such nevus cells.

POSTINFLAMMATORY MELANOSIS RESEMBLING URTICARIA PIGMENTOSA. Presented by DR. SAMUEL E. SWEITZER, Minneapolis, and DR. ELMER M. RUSTEN, Minneapolis.

Mrs. H. O., aged 30, states that she noted an eruption in December 1935, while she was hospitalized for a gynecological operation. The lesions began as erythematous macules on her arms and gradually spread over her trunk. During the following month the lesions turned brown. She has always taken a large variety of medicaments, including derivatives of acetylsalicylic acid, codeine and phenolphthalein. All these preparations have been given while the patient was under observation, and there has been no apparent effect on the eruption. She has had occasional attacks of urticaria which, she thought, were caused by glycyrrhiza.

The arms, the chest, the back and the upper portion of the abdomen are involved by the eruption, which is made up of small discrete pigmented macules. At times dermographism has been present, and the lesions have urticated after friction was applied.

The Wassermann, Rytz and Kahn tests of the blood have repeatedly given negative results.

Sections are shown. They reveal an increase of melanotic pigmentation in the basal cells. Numerous chromatophores are also present. No mast cells are seen.

DISCUSSION

DR. OLIVER S. ORMSBY, Chicago: Practically all the pigmentations seen in the skin after inflammatory lesions or neoplasms and due to deposits of pigment are caused by melanin. A second type of pigmentation is due to deposits of extraneous material, such as silver, mercury, bismuth or gold. The condition exhibited by this patient is of the first type. I wish to call attention to a peculiar type of pigmentation. Recently I saw a tuberculous patient with pigmentation which at a distance suggested argyria. There was a grayish discoloration on the exposed portions of the skin, including the face, which was particularly marked at the sides of the nose, on the forehead, on the dorsum of the hands and on the forearms. Addison's disease and argyria were excluded. Under the title "chrysocyanosis" there have been recorded abroad a number of cases of a similar discoloration of the skin in exposed areas developing after injection of large amounts of gold salts given in treatment of pulmonary tuberculosis. Emphasis is placed in these cases on the peculiar ashy gray or lilac tinted discoloration which begins in the ciliary margins and extends over the lids, face, forehead and other exposed parts. In the sanatorium for tuberculosis from which this report emanated every patient who received 15 Gm. or more of gold salts exhibited this peculiar type of pigmentation. Histologic examination showed particles of gold deposited in the skin.

DR. S. W. BECKER, Chicago: I agree with the diagnosis of postinflammatory melanosis, although it is impossible to state what the original eruption was. The sections show considerable pigment in the chromatophores; this probably accounts for the observations. Some years ago Miescher, of Zurich, Switzerland, reported that he injected melanin into vitiliginous patches and several years later observed considerable melanin in the histiocytic cells. In some persons pigmentation develops after any of the exanthems or other type of inflammatory lesions, while in others pigmentation does not appear at all.

LICHEN PLANUS; LOCALIZED AMYLOIDOSIS. Presented by DR. SAMUEL E. SWEITZER, Minneapolis, and DR. L. H. WINER, Minneapolis.

Mr. F. U., aged 64, states that his present eruption began below his left knee in the summer of 1935, appearing as pruritic papules. He repeatedly excoriated the lesions, and they gradually increased in size. During the summer of 1936 he was given roentgen therapy and noted marked relief of the pruritus.

On the lateral surface of the left leg just below the knee there is a lichenified violaceous plaque measuring 5 by 7 cm. Surrounding this lesion is an area of hyperpigmented and thickened skin which has the appearance of "pig skin," being characterized by large dilated follicles.

The Wassermann, Kahn and Rytz tests of the blood gave negative results.

Two sections are shown, one from the plaque stained with hematoxylin and eosin and one from the surrounding area stained with methyl violet.

DISCUSSION

DR. RUBEN NOMLAND, Iowa City, Iowa: I believe that this patient has only one disorder, localized amyloidosis, and that the apparent lichen planus is a simple inflammatory lesion which can, but usually does not, occur around an amyloid infiltration of the skin. Clinically it is almost impossible to differentiate certain forms of lichen planus and other lichenified lesions of the leg from localized amyloidosis occurring there. In this case the smallest and earliest lesion of localized amyloidosis was a pinhead-sized papule at the opening of a hair follicle. When this papule enlarges it closely simulates the papule of lichen planus, but in its early phase it does not. This smallest lesion of localized amyloidosis often serves to differentiate the eruption from other lichenified lesions of the leg. In this case the final diagnosis still needs microscopic verification.

The value of the local test with congo red with specific red staining of the amyloid lesions has recently been confirmed by Marchionini and John (Ueber lichenoide und poikilodermieartige Hautamyloidose, *Arch. f. Dermat. u. Syph.* **173**:545 [Feb.] 1936).

DR. L. H. WINER, Minneapolis: When my colleagues and I first saw this man in March he presented a lesion made up of violet papules which were quite discrete, and we made a clinical diagnosis of lichen planus. Microscopically the tissues showed hyperkeratosis, obliteration of the rete pegs of the epidermis and lymphocytic infiltrate in the upper portion of the dermis with a sharp border at the lower margin of the infiltrate. We treated him with roentgen therapy because he complained of severe pruritus. We did not see the patient again until the middle of August. At that time in addition to the original violet papules he also showed milky white papules the size of the head of a match. A biopsy was made, and amyloid was seen with gentian violet stain. Then we injected a solution of congo red intradermally into the whole area; this accounts for the discoloration seen today on the entire lower portion of the leg. We again examined the original sections and on careful study noted a faint trace of amyloid in them, but not enough to justify a diagnosis of amyloid. Dr. Bell and I prepared the original slides as well as those in which amyloid was observed, and we noticed a marked difference in the two sets of sections.

DR. JOHN F. MADDEN, St. Paul: I think it is impossible in many instances to differentiate clinically hypertrophic lichen planus of long standing, lichen chronicus simplex and localized amyloidosis. In such cases a biopsy should be made and the tissue should be examined for amyloid, the presence of which may be the most important factor in the resistance to treatment.

A CASE FOR DIAGNOSIS (TELANGIECTASIA MACULARIS ERUPTIVA PERSTANS?). Presented by Dr. H. E. MICHELSON, Minneapolis, and DR. F. W. LYNCH, St. Paul.

Mrs. V. E., aged 31, of Scandinavian descent, in 1917 first noticed pain and cyanosis of the hands on exposure to cold. In 1928 red "spots" developed on her

face, and since then there has been a gradual increase of these lesions on the chest, arms and face. During the winter of 1934 painful nodules developed on the posterior portions of the legs. These have never broken down but appeared spontaneously in two or three months and recurred at various intervals. The patient has had generalized pruritus for about nine years; it is usually nocturnal and is not associated with cutaneous lesions. No family history of tuberculosis can be elicited.

Hundreds of pale red lesions, varying from several millimeters to 1 cm. in diameter are scattered over the face and upper portion of the trunk. Smaller lesions are present on the tongue and palate. The cutaneous lesions disappear on pressure. On the chest and back are numerous atrophic scars resulting from excoriations. Each ankle presents hyperpigmentation and induration, and there are several deep indurated lesions on the calves.

The Mantoux test gave negative results with 1:10,000 and 1:100 dilutions of tuberculin.

Roentgenograms of the hands revealed narrowing of the articulate cartilages; no other abnormality was found.

DISCUSSION

Dr. S. W. Becker, Chicago: This case is interesting. I am inclined to agree with the diagnosis, although all these generalized telangiectasias are simply symptoms of some underlying condition. These conditions, I think, may be divided into two groups, the first of which is that of functional disorders. This patient's condition started with pallor of the fingers, a manifestation resembling the Raynaud syndrome. Adson has expressed the opinion that the impulses which result in the spasm of Raynaud's disease have their origin in the cerebrum. On the basis of studies on the neurodermatoses at the University of Chicago (van de Erve, John M., and Becker, S. W.: Functional Studies in Patients with the Neurodermatoses, *J. A. M. A.* **105**:1098 [Oct. 5] 1935) my colleagues and I believe that all functional diseases have their origin in cerebral hyperactivity. This patient has had generalized pruritus for nine years. When she was carefully questioned she stated that this is present after she undresses at night, a feature which is characteristic of functional pruritus. She has a painful nodule on the calf, so she has a definite infectious lesion on the leg. She has several devitalized teeth, any one of which may be the source of this infection. In studying the telangiectasia per se one notices that when the lesions are stroked the color returns quickly and is of the livid hue of venous blood. Ehrmann has called attention to the fact that when the blood returns quickly and the lesion is of venous hue there are usually vascular changes which are the result of infection. I believe that this woman's condition is due to infection which may be arising in her devitalized teeth, although there is ample evidence of functional disease.

Dr. Chester A. Doty, Detroit: In regard to what Dr. Becker said regarding devitalized teeth, I wish to state that I have cultured about 2,000 devitalized teeth which showed no abnormalities when examined roentgenologically. A large percentage of these revealed Streptococcus viridans. I agree with Dr. Becker that the vascular infections are probably of streptococcic origin. I feel that this patient's condition is due to a focal streptococcic infection probably originating in the devitalized teeth.

Dr. F. W. Lynch, St. Paul: It is interesting to note that this telangiectasia has remained practically unchanged for eight or nine years. One would have expected to see clinical variations depending on changes in the underlying factor, particularly if this factor is an infection. In previous cases of this disease described by F. Parkes Weber, Brocq and others there has been involvement of the trunk and extremities, but the face has remained free. In spite of the atypical localization in this case, I believe that the condition should be classified with that described by the aforementioned authors.

Sept. 13, 1936

PAUL A. O'LEARY, M.D., *in the Chair*

THRUSH OF THE SKIN AND MUCOUS MEMBRANE.*

J. E. H., an American boy aged 6 years, presents a dermatosis of the hands, feet, face and mouth. In the summer of 1932 the child mashed his left thumb in a screen door, after which the nail came off and regrew black and thickened. Shortly after that it was noted that the other finger-nails were turning black and that a circinate vesicular bordered eruption began at the base of the nails and gradually spread up the fingers, involving the back of the hands and the palms. Early in 1934 the nail of the right large toe turned black, and gradually the other toe-nails became black and thickened. In the autumn of 1934 the mother noticed a few lesions in the scalp and multiple areas of alopecia areata. At about Dec. 25, 1935, the child had a marked flare-up of all the cutaneous lesions, associated with chills, fever and loss of weight. The lesions were greatly inflamed; at that time lesions having the same characteristics as those on the hands appeared on the face.

During the first few years of its life the child had an intermittent diarrhea which was severe at times. He had whooping cough at the age of 4 years and mumps at the age of 5½ years. He has never been healthy. The mother noticed whitish areas, which may have been lesions of thrush, in the mouth since the patient was an infant.

The mouth shows whitish striae over the entire mucous membrane. The nails of both hands and feet are dark and markedly thickened. The fingers and toes, a part of the dorsum of the feet, the palms, the dorsum of the hands and the central area of the face show multiple circinate and annular vesicopustular lesions and scaling. The extension is from the terminal digits up on the palms and soles. The general examination gave negative results.

Cultures of material from lesions on the hand on dextrose broth and tartaric acid showed Monilia albicans. Cultures of the stools and sputum were reported to be negative for Monilia albicans. The serologic tests of the blood gave negative results. The sugar content of the blood was 80 mg. per hundred cubic centimeters.

A roentgenogram of the chest revealed calcification of the hilus of each lung.

A biopsy was not made.

DISCUSSION

DR. THEODORE CORNBLEET, Chicago: To me this case is instructive as demonstrating the different distribution of yeast infection in a child as compared to that in an adult. Apparently the secretions on the child's face lend themselves to the growth of yeasts whereas in adults the folds of skin tend to harbor more sugar-reducing substances and apparently for that reason are the sites for growing yeasts. The mucous membranes apparently change little from childhood to adult life, for they remain favorable sites for growing yeasts.

ECZEMA SOLARE.

G. H., a Jewish boy aged 3½ years, a midget, at the age of 1 year exhibited "redness" of both cheeks which extended over the nose. Almost complete fading occurred in the autumn, but there was a recurrence the following spring, and this course repeated itself the following year.

In August 1936 bright erythematous patches appeared on the cheeks and united across the bridge of the nose. On the forehead, neck, scalp and ears were bright erythematous small macules; suggestive atrophy was present in some lesions. There are circumscribed, elevated, pinkish, lichenoid plaques on the dorsum of the hands. Some "silvering" is present on the lower lip. The mother is of the opinion that exposure to sunlight aggravates the eruption.

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*This and the following presentations were made by Drs. Paul A. O'Leary, Hamilton Montgomery, Louis A. Brunsting and Richard J. Bailey, members of the dermatologic staff of the Mayo Clinic, Rochester, Minn.

Examination of the blood and urine gave negative results.

Roentgen examination gave the following results: The chest showed no abnormalities; the sella turcica was normal; the wrists showed two centers of ossification in each wrist which were apparently due to delayed development.

The tuberculin test gave negative results. The results of porphyrine tests on the urine and stool were within normal limits. Scratch tests with foods and inhalants gave negative results.

On Aug. 28, 1936, biopsy of a specimen from the hand showed an eczematoid type of reaction but no evidence of lupus erythematosus or lichen planus.

DISCUSSION

DR. JOHN F. MADDEN, St. Paul: In spite of the absence of typical histologic changes I think that the diagnosis of lupus erythematosus must be considered because of the location of the lesions—especially because of their presence behind the ears and on the mucous membrane of the lips—and of the apparent atrophic scarring seen in some of the lesions on the hands.

DR. OLIVER S. ORMSBY, Chicago: Many years ago I saw a young child who presented similar symptoms, and I hesitated for a time to class the condition as lupus erythematosus, but after two or three years' observation the diagnosis became clear. Several years later this patient was presented before the Chicago Dermatological Society; the condition had largely cleared up with the use of gold sodium thiosulfate. I think there is little doubt that this patient has lupus erythematosus.

DR. S. W. BECKER, Chicago: I am much impressed by this case for I have been studying a group of patients with summer prurigo, and I am inclined to place this patient's condition in that group. The child has a large amount of nervous instability, which characterizes all patients with that condition. The disorder started in the spring when the patient was about 1 year old, and this year it appeared in April before the ultraviolet rays of the sun became strong. Urbach in testing the skin of persons with that condition by filtered light found that the long and not the short waves produce summer prurigo. The disorder often tends to clear up in August, when ultraviolet rays are still present in large quantity. I do not believe that eczema solare is a good name for these lesions for lesions caused by eczema solare are more diffuse and vesicular. The absence of porphyrine is characteristic of summer prurigo. Further observation will, of course, determine whether or not the condition is lupus erythematosus.

DR. PAUL A. O'LEARY, Rochester, Minn.: My colleagues and I are of the same opinion as Dr. Becker. When the child was first seen lupus erythematosus seemed the most plausible diagnosis, but while he was in the hospital the lesions have undergone involution quite rapidly as a result of hospitalization alone. The patient exhibits the seasonal variation which Dr. Becker mentioned—the disorder practically disappears in the winter, leaving no atrophy. Histologic study showed no evidence of lupus erythematosus.

NEVOXANTHO-ENDOTHELIOMA.

J. W. M., a boy aged 11 months, presents smooth elevated firm brownish yellow nodules from 2 to 7 mm. in diameter on the medial surface of the right leg and thigh above the knee. At birth there were three small nodules on the right leg, two of which slowly underwent involution. The third nodule was excised shortly after the child's birth, and in the vicinity of the excision scar five small lesions appeared. Except for this observation the general physical examination gave essentially negative results. The results of laboratory studies of the sugar, fatty acids, cholesterol and total lipoids content of the blood were within normal limits.

Biopsy of material from one of the lesions showed a picture of nevoxanthoendothelioma with proliferation of the endothelial cells of the blood vessels to form endothelial giant cells; there were typical intracellular and extracellular deposits of lipoid, xanthoma cells and Touton giant cells.

A decrease in the fat content of the diet has resulted in softening of some of the lesions, but new lesions have continued to appear.

DISCUSSION

DR. MARCUS R. CARO, Chicago: The clinical picture in this case is identical with that in the case reported by Dr. Senear and me (ARCH. DERMAT. & SYPH. **34**:195 [Aug.] 1936). The histologic examination in our case showed many histiocytes containing varying amounts of lipoids and many giant cells, but no cells that we could identify as endothelial giant cells were observed. I think that the presence of endothelial giant cells in this case justifies one in classifying the condition as nevoxantho-endothelioma and in distinguishing it from the ordinary form of juvenile xanthoma.

DR. L. H. WINER, Minneapolis: In regard to the recognition of endothelial cells as such, eminent pathologists cannot identify an endothelial cell as such from its morphologic appearance alone. The only time they can recognize endothelial cells is when the cell takes on structure of endothelium-forming capillaries. For that reason the word "endothelioma" as a part of this name should be either eliminated or considered further. The section, showing Touton giant cells and fibroblasts, suggests one of the forms of juvenile or infantile xanthoma.

DR. EVERETT S. LAIN, Oklahoma City: I was especially interested in this case, for my co-workers and I have been observing a case of nevoxantho-endothelioma for more than five years. Our case was presented at the meeting in Kansas City, Mo., three years ago. At that time the diagnosis was uncertain. The condition had been variously diagnosed as lymphoblastoma, endothelioma and neurofibroma. In our case the manifestations are so striking and the history is so spectacular that the case has almost become famous. The lesions appeared when the patient was 2 weeks of age; soon thereafter there was a gradual rise of temperature which continued, the temperature being from 102 to 106 F. for eighteen months. Roentgenograms showed multiple lesions in the chest and throughout the abdominal cavity. Although they could not be demonstrated, tumors were doubtless present inside the skull. We were finally aided in making a diagnosis by the article of McDonagh (*Brit. J. Dermat.* **23**:115, 1911). The tumors all over the body are now slowly undergoing spontaneous involution after they had previously resisted all kinds of treatment. Each tumor as it disappears leaves a white atrophic depressed scar. Our case will be reported fully by Dr. John H. Lamb at the meeting of the Southern Medical Association.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Nevoxantho-endothelioma usually develops at birth, and after a period of months or years the lesions usually undergo spontaneous involution, which is in contrast to what happens in cases of xanthoma. True endothelioma cutis was described as a malignant tumor a few years ago, but some pathologists are unwilling to accept such a diagnosis. In this case the sections show endothelial cells forming new capillaries and also endothelial giant cells. Little or no fat is seen in these cells in contrast to the marked deposits of fat in the various histiocytes, including the xanthoma or foam cells and the Touton giant cells. I think that the clinical and histologic pictures justify the diagnosis. McDonagh's term is a descriptive one and, to be strictly accurate, one could refer to the condition as nevoxanthoma with endothelial proliferation. The presence of endothelial giant cells serves to distinguish this condition from ordinary juvenile xanthoma.

DR. PAUL A. O'LEARY, Rochester, Minn.: The lesions have undergone about 50 per cent involution since a diet with a marked reduction in the fat intake was prescribed.

ANGIOMA SERPIGINOSUM.

E. K., a German woman aged 32, states that an eruption developed on her left ankle in April 1936. Injections into some varicose veins of the left leg were made shortly thereafter. The eruption spread to the other ankle and within two months involved both legs from the foot to the middle portion of the thigh. There is no pruritus or rheumatic pain.

The patient received injections for varicose veins in 1930 and obtained relief. There are a mild edema and moderate varicosities of both legs.

She presents a markedly symmetrical eruption on the lower extremities; it extends from the sole of each foot to the middle of the thigh. The older lesions, located about the lower half of the legs, consist of isolated and grouped reddish puncta. Some of these plaques show areas of central atrophy. On the soles and in the region from the knee upward numerous pinkish rings are seen; some of these are arranged in serpiginous outline. The lesions do not fade on pressure. Areas of hyperpigmentation and extravasation of blood are present about the ankles.

Urinalysis and flocculation tests gave negative results. The blood picture shows mild secondary anemia; the number of platelets was 127,000, the bleeding time three and a half minutes, and the coagulation time seven minutes; the clot retractility was marked at the end of two hours and complete at the end of four and a half hours. A special blood smear revealed no immaturity of leukocytes.

Biopsy revealed changes consistent with the diagnosis of angioma serpiginosum. The absence of deposits of hemosiderin ruled out Schamberg's disease and the various purpuras. The sections showed early changes consistent with the clinical diagnosis of angioma serpiginosum. Parakeratosis was not noted in any of the sections.

DISCUSSION

DR. S. W. BECKER, Chicago: I am interested in this case because I think this is the first case of angioma serpiginosum I have ever had an opportunity to observe. If the condition exhibited by this patient is angioma serpiginosum I think it has a misleading name. There is nothing to suggest angioma. On section some vascular dilatation and obliteration with diapedesis of red blood cells are observed. Clinically it is impossible to express any of the blood with the diascope. The eruption seems to be a reticular form of thrombotic purpura rather than a real angioma.

DR. H. E. MICHELSON, Minneapolis: I did not get the impression that this is a purpuric process. I feel that it is essentially an ectatic one. I think that the capillaries are decidedly dilated and that the whole picture comes as near the original description as any I have seen.

DR. H. R. FOERSTER, Milwaukee: I believe that the possibility of Majocchi's disease (purpura annularis telangiectodes) should receive consideration in this case because of the type of vascular lesions, the annular configuration and the localization. Purpura is not always demonstrable in Majocchi's disease.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: This is not a purpura. Various types of purpura as well as Schamberg's disease show deposits of hemosiderin, and such deposits cannot be demonstrated in angioma serpiginosum. In the latter there are capillaries filled with blood cells and some dilated and newly formed capillaries. I believe that in this case the condition represents an earlier stage of the same pathologic process as that which was present in the case which was presented at the meeting of the Minnesota Dermatological Society, on July 28, 1934 (ARCH. DERMAT. & SYPH. **31**:412 [March] 1935), and which Dr. Bailey and I recently reported. In at least two of the cases reported in the literature the condition has undergone spontaneous involution.

FIBROMYXOSARCOMA.

Mr. L. S., aged 74, a German, states that about six months ago tumors appeared on the lower portion of his left leg. At that time he noticed nodules in a bruised and pigmented area which had been present since he was 22, at which time that part of the leg was traumatized while the patient was exercising in a gymnasium. The nodules have gradually grown larger above the ankle, and during the past three months a large mass has appeared over the upper anterior part of the tibia, so that the left leg is almost twice the size of the right. There is no history of pigmented nevi having previously been present in this area.

The portion of the left leg between the ankle and the knee, largely on the anterior aspect, shows multiple firm pinkish fungating nodules. These lesions, especially in the upper part, seem to come from beneath the skin proper, making the overlying skin tense and glistening. Below, the nodules project over the skin and show some ulceration. They vary in size from that of a small pea to that of a walnut, and many of them are conglomerate. There is grade I to II edema of the ankle, and in the inguinal region there is adenopathy.

Physical examination revealed arteriosclerotic heart disease and prostatic hypertrophy of grade III.

A roentgenogram of the left leg showed osteoperiostitis of the middle third of the shaft of the tibia.

Biopsy revealed a picture of fibromyxosarcoma.

Treatment has consisted of roentgen therapy.

TUBERCULOSIS CUTIS FOLLICULARIS DISSEMINATA.

CASE 1.—Mrs. E. F. H., aged 39, says that in the winter of 1935-1936 an eruption gradually developed on the face and was soon followed by the appearance of similar lesions on the arms. The condition has remained practically stationary since the onset, and the general health has been unchanged.

Practically localized to the forehead and cheeks are discrete slightly elevated erythematous papules showing a change of color in the center which yields an apple jelly hue on pressure with the diascope. Similar lesions are present on the arms.

Urinalysis and flocculation tests of the blood gave negative results. Examination of the blood revealed 4,550,000 erythrocytes, 8,400 leukocytes and 94 per cent hemoglobin. Intradermal tests with tuberculin gave negative results with a weak and positive results with a strong dilution of purified protein derivative.

A roentgenogram of the chest showed no abnormalities.

Biopsy revealed a picture consistent with hematogenous tuberculosis; there was little caseation necrosis as compared with that observed in most cases of tuberculosis cutis follicularis disseminata; the histologic picture was more suggestive of rosacea-like tuberculid of Lewandowsky.

Treatment has consisted of gold sodium thiosulfate in the following dosages: 15 mg., one injection; 25 mg., three injections; 35 mg., six injections; 50 mg., six injections. Two weeks ago an erythematous eruption developed while the patient was receiving treatment with a gold preparation at home.

CASE 2.—Mr. O. W. J., aged 27, states that in August 1935 he noted swellings at the angle of the jaw on both sides; this persisted for from three to four weeks. After this attack numerous shot-sized papules, some of which were pustular, appeared on his chin, forehead and cheeks. In December 1935 the glandular swellings recurred. There was no pain or fever, but the patient experienced general malaise. He was given three treatments with roentgen rays to the glands a month before he presented himself at the Mayo Clinic.

Firm nontender swellings are present at the angles of the mandible on both sides and in the preauricular region. Numerous shot-sized firm papules of various shapes and some pustules are scattered over the face and grouped on the chin, forehead and lower eyelids. There is considerable erythema, and dry desquamation of the face is present.

Urinalysis, flocculation tests, blood counts and determinations of the hemoglobin content gave normal results. Roentgenograms of the chest showed no abnormalities. An intradermal test with tuberculin, a weak purified protein derivative being used, gave negative results.

Biopsy revealed a typical picture of tuberculosis cutis follicularis disseminata.

Treatment has consisted of intradermal injections of a purified protein derivative of tuberculin, the original dose consisting of 0.1 cc. of a weak dilution (1:10) and the dosage being increased until the seventh injection, which consisted of 0.1 cc. of a strong dilution. Administration of old tuberculin was then started, 0.1 cc. of a 1:1,000 dilution being given. This dosage was repeated once, and then the

patient was given 0.1 cc. of a 1:750 dilution. He went home for four months and returned showing 50 per cent improvement; he received no treatment at home. He was then given injections of 0.07 cc. of a 1:750 dilution of old tuberculin.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: When one gets into the habit of discussing tuberculosis of the skin every time a case is shown it may appear as though he desired to carry on a controversy, but this is far from being my intention. I should like to know precisely what Dr. Montgomery means by the term "tuberculosis cutis follicularis disseminata." I think that in discussing tuberculosis of the skin when a good name has been used one should continue to use that name until a better one is found. For example, sarcoid. I believe, furthermore, that the use of a name should imply a definite condition, for instance, the term lupus miliaris dessiminatus faciei might be used to designate the condition in case 2 of this group. This condition is not strictly follicular although quite a few of the lesions are, and the clinical course, the pathology and the prognosis are the same in all the examples that I have seen. In case 1 I think the microscopic picture is that of sarcoid, and certainly the same terminology cannot be used in the two cases.

DR. OLIVER S. ORMSBY, Chicago: I think that Dr. Montgomery uses the term "tuberculosis cutis follicularis disseminata" as a generic term to designate cases in which the lesions are limited to the face and others in which lesions are present on the face and on other portions of the body. In case 1 the latter group of symptoms is present. Case 2 exemplifies a condition ordinarily classed as lupus miliaris disseminatus faciei, which is a well defined clinical entity.

DR. RUBEN NOMLAND, Iowa City, Iowa: The only thing I can say about tuberculosis of the papular type on the face is that there are four or five entities which, I think, can be differentiated by clinical and microscopic study. One can differentiate definitely lupus miliaris disseminatus faciei, miliary sarcoid, acne rosacea-like tuberculid and acnitis. In some cases microscopic examination is necessary to establish the differentiation, but I think that these four conditions can be distinguished from each other.

DR. CLARK W. FINNERUD, Chicago: In case 1, without having seen the history, I first thought of sarcoid, and that diagnosis was well borne out histologically. I think there are transitional forms which cannot be classified accurately, but in this instance I thought the condition was rather definitely sarcoid.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Lupus miliaris disseminatus is a poor term because the condition to which it refers has nothing in common with lupus vulgaris and the name is confusing to students. Lupus vulgaris spreads through the lymphatics, whereas lupus miliaris disseminatus (tuberculosis cutis follicularis disseminata) is a hematogenous form of tuberculosis showing an entirely different course and a different response to treatment. I agree that many of the lesions are not follicular, but the word follicularis is warranted just as much as in designating other conditions in which not all the lesions are follicular, namely, keratosis suprafollicularis. However, I have seen the picture of tuberculosis cutis follicularis disseminata limited to the legs. In the first case of tuberculosis cutis follicularis disseminata which was presented the histologic examination showed a sarcoid-like picture and failed to show caseation necrosis, so that from the histologic standpoint I preferred to classify the condition with rosacea-like tuberculid of Lewandowsky or disseminate sarcoid. All dermatologists are familiar with the great variation in types of sarcoid which may be present in the same person. Hence, in my classification of tuberculosis (scientific exhibit, Eighty-Seventh Annual Session of the American Medical Association, 1936) these have all been grouped closely together, though until more is known about tuberculosis of the skin it is well to keep some of the older subdivisions, if only from the standpoint of prognosis and treatment. I do not deny that in rare instances the granuloma of lupus vulgaris may cause erosion of the blood vessels and give rise to hematogenous dissemination, but in the great majority of cases of lupus vulgaris the spread is only by local extension through the lymphatics.

ATOPIC ECZEMA WITH CATARACTS.

Mrs. E. D. E., aged 33, states that since she was 3 years old she had a cutaneous condition involving the face, the neck, the arms, the back of the hands and particularly the flexures of the elbows. At first the condition improved in the summer and flared up in the winter, but during the past few years it has remained constant, paroxysms of pruritus occurring. It has been aggravated when the patient ate eggs and oatmeal and when she came in contact with silk. She has had two attacks of asthma lasting half a day; these occurred immediately after the birth of her two children. During the past three years she has had irregular attacks of wheezing lasting from one to two hours. She complains of almost constant "stuffiness" of the nose. When she was 25 there was cloudiness of vision in the right eye for three months after the birth of her first child, the condition rapidly progressing to almost complete loss of vision. She is not aware of a defect in the left eye.

A dry lichenified scaling dermatitis involves the eyelids, the face, the neck, the upper portion of the chest, the breasts, the antecubital spaces and the popliteal fossae. Examination of the eyes gave the following results: The right eye showed a mature cataract, the left showed scattered opacities of the lens and central posterior capsular opacity.

A roentgenogram of the chest revealed questionable tuberculous activity at the apex of the right lung.

Intradermal tests gave the following results:

4 Plus Reactions	3 Plus Reactions	2 Plus Reactions
Silk	Ragweed (mixed)	Orris
Rabbit hair	Dog hair	Horse hair
Whole wheat	Cattle hair	Corn
	Cat hair	Lamb
	Oats	Pineapple
	Whole egg	
	Pork	
	Potato	

A biopsy has not been made.

Treatment has consisted of autohematherapy, elimination diets, colloid baths and application of mild unguents and pastes. Tar and sulfonated bitumen are not tolerated.

SENSITIVITY TO UREASE.

Miss M. D., a laboratory technician aged 31, during the past ten years has had attacks of sneezing occurring irregularly in the morning and lasting for one or two hours; the etiology is unknown. There has been no seasonal variation. During the past ten months she has had five attacks of swelling, redness and watering of the left eye. The onset of each attack occurred between eight and nine o'clock in the morning, and the attack lasted for two or three hours. She is not certain about swelling of the eyelids. A month ago the cheeks, upper lip and eyelids became so swollen that she was unable to see. The attack lasted for two hours and subsided slowly during the ensuing twenty-four hours. On Sept. 3, 1936, she had another flare-up of conjunctivitis and swelling of the lids of the left eye. This attack followed the weighing out of powdered urease in the laboratory of the Mayo Clinic. She does not suffer from urticaria, migraine, asthma or eczema. She states that she does not take any internal medication and that as far as she knows the flare-ups are not associated with dietary factors.

No cutaneous lesions were present when the patient was first seen. On Sept. 4, 1936, a 1 per cent aqueous solution of urease was prepared; 1 drop was placed in the left eye of the patient and 1 drop in Dr. Brunsting's left eye. Within from ten to fifteen minutes there was a marked typical reaction in the conjunctiva and lids of the patient's eye, but no reaction occurred in the eye of the control.

Roentgenograms of the sinuses revealed a thickened membrane and a cyst in the floor of the left sinus. Intracutaneous tests showed a 2 plus reaction to orris.

A biopsy has not been made.

SENSITIVITY TO SALIGENIN (SALICYL ALCOHOL), A LOCAL ANESTHETIC USED IN IODOBISMITOL (SQUIBB).

Mr. J. R. P., a Polish-American saloon owner aged 48, states that he had a chancre at the age of 22. On March 25 and on March 27, 1936, he was given an intramuscular injection of 2.0 cc. of iodobismitol, and within twenty-four hours after the treatment urticarial lesions with beginning vesiculation were noted on each hip about the site of the injection, the reaction being more pronounced on the right than on the left hip. Some edema was present.

Examination of the blood and cerebrospinal fluid revealed evidence of syphilis.

The results of patch tests were as follows: A test with iodobismitol with saligenin (Squibb) gave a positive reaction; a test with iodobismitol without saligenin (Squibb), a negative reaction; one with saligenin in propylene glycol, a positive reaction; one with propylene glycol, a negative reaction. Numerous other patch tests with various bismuth preparations gave negative results.

The composition of iodobismitol as given by Squibb is as follows:

Sodium iodobismuthite	0.12 Gm. (6%)
Sodium iodide	0.24 Gm. (12%)
Saligenin (salicyl alcohol)	0.08 Gm. (4%)
Propylene glycol	2.00 cc.

Treatment has been continued with a bismuth preparation which did not contain saligenin, and no ill effects have been noted.

DISCUSSION

DR. CLARK W. FINNERUD, Chicago: The case of sensitivity to saligenin interests me as it is the third case of this type of sensitivity that I have observed. In the other two cases iodobismitol also produced the disorder. The lesions occurred within a day after the injection and involved a large portion of the buttock in an inflammatory reaction resembling a cellulitis. It was not aware what part of the preparation caused the reaction. It is interesting to learn that it is the saligenin contained in the preparation.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: The case of eczema associated with cataract is interesting because of the relationship of cataract to the atopic state, and a question is raised by ophthalmologists as to whether the cataracts are due to the actinic rays of the ultraviolet lamp or to the roentgen rays, to which most patients with this condition have been exposed. Benedict expressed the conviction that the cataract is of a distinct type and different from cataracts resulting from exposure to roentgen rays. Furthermore, cataracts of this type have developed in patients who had received no roentgen therapy and who had had the eyes covered when ultraviolet radiation was administered. Likewise, ultraviolet and roentgen radiation are used in many different cutaneous diseases and this type of cataract is not seen in cases of cutaneous conditions other than that under consideration except occasionally in scleroderma. My co-workers and I are inclined to believe that the changes in the lens are a part of the systemic reaction in a hypersensitive person (ARCH. DERMAT. & SYPH. **34**:935-954 [Dec.] 1936).

I wish to mention something in regard to the unusual manifestation in the second case in this group, that of the laboratory technician with the ophthalmic urticarial reaction to urease. She has consulted us six or eight times during the past year because of recurrent swelling of the left eye and eyelids. We tried to relate the condition to some extraneous material but were not successful. The symptoms usually occur in the left eye, but occasionally they appear in the right eye. The patient has been weighing powdered urease in the laboratory frequently, and a few days ago she suggested that the powder might be the cause of the trouble. A drop of a dilute solution of urease instilled in the eye produced a prompt and severe urticarial reaction. Patch tests with urease gave negative results. There was a positive reaction to a scratch test with this powder and to a test with orris.

MONOCYTIC LEUKEMIA (LEUKEMIC RETICULO-ENDOTHELIOSIS).

Mr. N. G. Z., a retired butcher aged 63, states that the onset of his cutaneous condition occurred in March 1931, when dryness, slight scaling and pruritus of the medial aspects of the thighs and of the flexor surfaces of the upper extremities developed. In July 1931 he noted increasing thickness, scaling and cracking of the palms and soles. The extent and severity of the disorder showed moderate fluctuation, but the condition never disappeared. In December 1935 it became much worse; the skin was red, thickened and scaly.

In April 1935 there were generalized mild thickening and lichenification of the skin, numerous scattered superficial large ill defined dry scaling eczematous plaques and marked lamellar hyperkeratosis with fissuring of the palms and soles. At this time the clinical picture was suggestive of mycosis fungoides. In June 1936 the clinical picture was that of an exfoliative dermatitis. There was moderate inguinal lymphadenopathy.

Flocculation tests and urinalysis gave negative results. Roentgenograms of the chest showed no abnormalities.

Study of the blood gave the following results:

	April 8, 1935	June 10, 1936
Erythrocytes	4,230,000	3,720,000
Leukocytes	13,300	21,300
Hemoglobin	95.0%	70.0%
Lymphocytes	20.0%	25.0%
Monocytes	1.5%	1.0%
Neutrophils	50.0%	26.0%
Eosinophils	0.5%	
Cells of reticular origin	28.0%	48.0%

Dr. Watkins, the hematologist, reported that on April 8, 1935, the lymphocyte picture was unusual but not diagnostic; large nuclei with indented portions were present. By June 1936 there was leukemic reticulo-endotheliosis of chronic type with lymphocytes showing a peculiar grooving, resembling most the cells of salamanders.

A biopsy made in April 1935 revealed many features of mycosis fungoides with quite a number of lymphocyte-like cells exhibiting notched serration and grooving of the nuclei; these cells were identical with cells seen in touch smears from biopsy material and in blood smears.

In June 1936 a biopsy showed the infiltrate in the upper portion of the cutis to be denser; many definite monocytic cells (Schilling) showing indentation and grooving of the nuclei were observed.

Treatment has consisted of roentgen therapy; in April 1935 high voltage irradiation to gland-bearing areas was given; it resulted in considerable reduction of the pruritus. In June 1936 superficial irradiation was given to the entire cutaneous surface. The patient has also received colloid baths and local symptomatic treatment. There has been a marked improvement in the condition of the skin, only a slight erythroderma with a little scaling remaining.

DISCUSSION

DR. OLIVER S. ORMSBY, Chicago: This patient states that I saw him about five years ago, but I have no recollection of his case. The symptoms at present are those of general exfoliative dermatitis. Considering the past and present cutaneous symptoms together with the blood picture the condition belongs in the group of lymphoblastoma with a leukemic foundation.

DR. F. W. LYNCH, St. Paul: Specific erythroderma is an uncommon manifestation of leukemia, but it has been recognized for many years. I believe this is the first instance in which monocytic leukemia has been recognized as a cause of erythroderma. It is interesting to note that over a year ago, when he was still unable to make a diagnosis, the hematologist stated that the blood picture was not normal. Such nonspecific changes were also observed in the early stages of monocytic leukemia and reticulo-endotheliosis in several of the cases which I reviewed.

GENERALIZED AND DIFFUSE SCLERODERMA.

Mr. C. F. R., a salesman aged 47, in the autumn of 1935 first noticed some puffiness and tightness in the hands; this was followed by hardening. At first the puffiness came on during the week-ends and disappeared during the ensuing week, and finally the hardening set in. A tonsillectomy performed on Dec. 13, 1935, was followed by an aggravation of symptoms in the hands and feet and puffiness and stiffness in the knees, ankles and face. There were also nausea and fatigue. Since then the puffiness has decreased and the stiffness has increased. The feet and hands have a bluish hue and are more sweaty now than formerly. The patient states that he feels better in hot than in cold weather. He has lost 40 pounds (18.1 Kg.) since the onset of the disorder and is troubled with bronchial secretion.

The patient's face is expressionless, and he shows evidence of loss of weight. The skin is yellowish brown, and over the face, hands, knees and feet it is firm and tensely drawn. The patient is unable to open his mouth or close his fist, and motion in the knees and ankles is limited. On the distal third of the penis is a band of sclerosis. Both hands and feet are sweaty, cold and slightly cyanotic. There is a suggestion of bronchiectasis in the base of both lungs.

A roentgenogram of the chest revealed localized bronchiectasis of the base of the left lung. Examination of the blood showed 4,600,000 erythrocytes, from 14,900 to 13,900 leukocytes and 90 per cent hemoglobin. The differential blood cell count gave the following results: polymorphonuclears, 52.5 per cent; lymphocytes, 28.5 per cent; monocytes, 6.5 per cent; eosinophils, 12.5 per cent.

Biopsy revealed changes consistent with scleroderma; the picture was not diagnostic. Cultures of muscular material were sterile after one week.

The patient has been given eight treatments of five hours each with a vapotherm unit, the temperature ranging from 103 to 105 F. He has shown 25 per cent improvement.

SCLERODERMA.

Mrs. F. S., a housewife aged 32, states that she has had numbness and blanching of the fingers and swelling of the feet, legs, hands and face, since October 1935. Pain in the knees on walking or climbing has been present since February 1936. In June 1936 she noted a "tightening" of the muscles of the hands and forearms. The hands became progressively stiffer and contracted. The skin over the forearms and face subsequently became tight, and the face felt numb. She has retained expression in the face and has no difficulty in swallowing, but there is some difficulty in opening the mouth and in protruding the tongue.

The patient has been married fifteen years and has six children. In 1929 she underwent a thyroidectomy, an appendectomy and a suspension of the uterus. In 1930 she underwent a tonsillectomy. All these operations were performed at other hospitals.

The skin over the face, forearms and hands is thickened, swollen, tight, glazed and smooth. The skin of the face is of ivory hue, and there is some ironing out of the features. The patient looks ill and is pale and thin. There is no evidence of Raynaud's disease or of hyperthyroidism.

The vasomotor index is good: The rise in temperature in the left toe was 2.5 F.; in the right toe there was a rise of 2.3 F.; in the left third finger the rise was 2.08 F., and in the right third finger it was 1.70 F.

The basal metabolic rate on Aug. 14, 1936, was + 56 per cent; on Aug. 18, 1936, it was + 47 per cent.

Biopsy revealed changes in the skin and muscle consistent with the picture of scleroderma.

DERMATOMYOSITIS.

CASE 1.—Mr. C. A. H., aged 45, an employee in a boot and shoe factory, where he works with aniline dyes, states that in November 1935 he noticed redness of the joints of his fingers. There was no pain or swelling in the joints.

Five weeks later similar red patches appeared on the eyelids and considerable puffiness was noted. The edema of the eyelids extended to involve the entire face, the neck, the shoulders, the legs, the ankles, the upper portion of the chest and both arms and hands to the finger tips. The process began to subside by May 1936. Progressive weakness was first noted in February 1936 and increased until the patient was unable to walk or even lift his hands to his face and could not sit up alone. There was some improvement after from three to four months, but much residual weakness remained. There has been aching of the muscles, especially when the patient attempts to move. He has difficulty in swallowing solid and semisolid food. There has been pigmentation of the face, hands, neck and chest; this was accentuated by roentgen therapy given between February and August 1936.

The patient states that he had diphtheria when he was a child and underwent a tonsillectomy at the age of 5. In March 1935 he had several attacks of severe sinus infection associated with much yellowish discharge. The condition persisted for about two months.

There is marked brownish pigmentation of the face, hands, chest and back, and the skin has a dusky cyanotic hue. Edema of the face and eyelids is most marked, but there is a moderate degree of edema over the entire body. The skin feels leathery and thickened. The muscles are hard and tender to pressure, and there is marked atrophy of the shoulder muscles. The patient is unable to move the arms or legs and is totally incapacitated.

Examination of the blood showed 4,150,000 erythrocytes, 7,900 leukocytes and 12.9 Gm. hemoglobin. The polymorphonuclear leukocytes showed a marked shift to the left. Flocculation tests gave negative results. The urea content of the blood was 18 mg. and the creatinine content, 1.1 mg., per hundred cubic centimeters. The serum contained 3.3 mg. of sulfates, and 3.7 mg. creatinine, per hundred cubic centimeters. The blood contained no methemoglobin. Culture of muscular material gave negative results; culture of material from the throat revealed green-producing diplostreptococci.

A roentgenogram of the sinus showed no abnormalities; those of the chest showed bronchiectasis on the right side.

Biopsy revealed changes in the muscles consistent with the clinical diagnosis of dermatomyositis; there was marked parenchymatous degeneration of muscle fibers.

CASE 2.—R. L. L., a boy aged 11 years, says that during the summer of 1935 he began to lose appetite, feel tired and listless and suffer from pain in his feet. His parents noted redness about the eyes and some scaling. In September the scaling became generalized (exfoliative dermatitis). There was a rise in temperature to 101 F., and soreness of the gums and swelling and inflammation of the fingers, ankles, knees and elbows developed. The patient was confined to bed until June 1936. In October 1935 at the State of Wisconsin General Hospital, Madison, Wis., a diagnosis of rheumatic fever, secondary anemia, exfoliative dermatitis and mild arsenical poisoning was made. The patient's father, a druggist, says that he does not have any knowledge of the boy's having received arsenic. The patient has continued to exhibit a rise in temperature up to 100 F. every afternoon up to the present time. In April 1936 when he was examined at the State of Wisconsin General Hospital, a diagnosis of trench mouth and rheumatoid arthritis was made. Typhoid vaccine and Clawson's streptococcus vaccine were given; this treatment was followed by improvement in the joints. In June 1936 the condition of the mouth became worse and the patient was given twelve injections of neoarsphenamine. The dermatitis recurred, and the child became irritable. He has noted stiffness in the muscles affecting the gait and progressively increasing disability.

The patient is pale and thin and appears ill. There is a generalized mild exfoliation associated with some erythema and some puffiness about the eyes. Palpation shows subcutaneous firmness over the entire body, although the skin itself feels fairly soft. There is atrophy of the muscles of the shoulder girdle, with limitation from fibrous contractions in the joints.

Examination of the blood showed 3,990,000 erythrocytes, 9,600 leukocytes and 68.4 per cent hemoglobin. Examination of the urine showed no arsenic. The results of the tuberculin test were negative. An agglutination test for Brucella abortus and paratyphoid organisms gave negative results; an agglutination test for Bacillus typhosus gave positive results in a dilution of 1 part of serum to 1,280 parts of saline solution.

Roentgenograms of the chest, bones and joints disclosed no abnormalities.

Biopsy of cutaneous material revealed hyperkeratosis and atrophy of the prickle cell layer and pyknosis and palisade arrangement of the basal cells of the epidermis, suggesting an arsenical pigmentation. Biopsy of muscular material revealed early parenchymatous changes consistent with dermatomyositis. Culture of muscular material gave negative results.

CASE 3.—A. E., a girl aged 9 years, in November 1935 exhibited redness of the eyelids and adjacent areas of the nose, the involvement extending to cover the cheeks. In January 1936 there developed swelling, redness and aching of the joints of the ankles and fingers. During the subsequent six months all the large joints became involved in turn and the erythema of the skin spread to the neck, upper portion of the chest and extensor surfaces in the region of the elbows and knees. Generalized aches and pains developed in the muscles of the limbs and back. There was a slight fever, and the patient lost some weight.

The child has been sick, weak and bedridden since January 1936. The face is puffy and expressionless. There is a diffuse erythema of the cheeks, eyelids and bridge of the nose, which is fairly sharply delimited, and when the erythema subsides atrophy is quite obvious. A similar process is noted on the anterior aspect of the neck, on the adjacent upper portion of the chest and over the extensor aspects of the extremities in the region of the elbows and knees. There is atrophy of the muscles of the shoulder girdle. The spleen is normal in size; the heart is normal. There is muscular weakness. The temperature has ranged from 100 to 101 F.

Flocculation tests of the blood and urinalysis gave negative results. Roentgenograms of the heart and lungs showed no abnormalities. The differential blood cell count showed a toxic reaction with few immature lymphocytes. The percentage of polymorphonuclears and that of leukocytes were within normal limits. Serum potential studies (Welsh) gave positive results for erythema multiforme and negative results for lupus erythematosus, dermatitis herpetiformis and pemphigus. The Mantoux test gave a questionable reaction.

The original clinical impression was acute disseminated lupus erythematosus, but the biopsy revealed a toxic dermatitis consistent with erythema multiforme; there was no evidence of lupus erythematosus.

DISCUSSION

DR. PAUL A. O'LEARY, Rochester, Minn.: Six patients with dermatomyositis have been observed during the past two months; however, two of them were unable to remain in town for this meeting, and one died. I am greatly disappointed that I am not able to present these two additional patients today because they exhibited different manifestations of the end-results of the disease. One of these patients, a boy aged 8 years, who has been observed by us for two years, within the last three months has presented signs of myositis ossificans. In the other patient, a young woman who has had the disease for ten years, the involvement is confined to the trunk and upper extremities and the disease is apparently in an arrested state. Her greatest difficulty is now noticed in swallowing and in breathing deeply.

In discussing the two cases of scleredema adultorum at Minneapolis yesterday I called attention to the difficulty in distinguishing between certain diseases of this group at the onset. In the cases presented today there are some of the varieties of the dermatologic pictures of dermatomyositis; in case 3 the condition resembles acute disseminated lupus erythematosus; in case 2 there still is evidence of the exfoliative dermatitis and in case 1 there is a diffuse pigmentation, the condition in

some respects resembling Addison's disease. The feature common in all these cases is the muscular involvement which is present in varying degrees, ranging from complete helplessness in case 1 to limitation of muscular function as in case 2. This feature of the clinical picture has necessitated the elimination of myasthenia gravis and progressive muscular dystrophy or atrophy in the differential diagnosis. This, I believe, has been done by biopsy of muscular tissue and by consultation with members of the staff of the Mayo Clinic who have had extensive experience with both of these diseases.

I believe that dermatomyositis is an infectious disease that involves primarily the musculature and that may present a variable dermatologic picture. In cases of acute involvement a diplostreptococcus has been obtained from a culture of muscular tissue while in cases in which the condition was of long standing repeated efforts to culture an organism from material from the muscle have been futile. Treatment has consisted of nonspecific therapy with typhoid vaccine, small doses being used because of the possibility of involvement of the cardiac muscle, administration of amino-acetic acid, massage, a high vitamin diet and oxygen therapy for from six to eight hours a day.

The two patients with scleroderma were presented merely to permit a comparison between scleroderma and dermatomyositis.

Hydrosadenitis Suppurativa (Verneuil).

Mr. W. A., aged 37, a truck driver, states that in 1930 he had what appeared to be a furuncle of the right axilla; this soon opened and drained spontaneously, forming numerous sinus tracts. Within a year a similar condition appeared in the left axilla and in the inguinal and perianal regions; this has persisted. Occasionally there has been fever; otherwise the general health has been unusually good.

The patient is well developed and robust and does not appear acutely ill. His present weight is 170 pounds (77.2 Kg.); his normal weight, 190 pounds (86.2 Kg.). There are draining sinuses in the axillae, groins and perineum.

Flocculation tests of the blood and urinalysis gave negative results. Tests with Frei antigen have repeatedly given negative results. A test with a purified protein derivative of tuberculin was also negative. Smears and culture of discharge from the sinuses showed no Mycobacterium tuberculosis, sulfur bodies or fungi. Examination of the blood showed 3,850,000 erythrocytes, 17,300 leukocytes and 92 per cent hemoglobin. The differential blood cell count gave normal results. A roentgenogram of the chest showed no abnormalities.

Biopsy of material from the right axilla revealed hidrosadenitis suppurativa (Verneuil); no evidence of tuberculosis was observed; there was marked involvement of apocrine glands with dense infiltrate predominantly plasma cell in character.

Treatment has consisted of symptomatic local measures, administration of neoarsphenamine, roentgen therapy and excision and cauterization of the involved area in the left axilla with subsequent skin grafting.

DISCUSSION

Dr. Paul A. O'Leary, Rochester, Minn.: This patient has been treated at the clinic for a year; medical measures were used, and temporary improvement resulted. When treatment was stopped he had a severe flare-up, and a large ischiac abscess developed. The results of surgical treatment, which consisted of cleaning out the axillae and making a full thickness skin graft, have been decidedly more encouraging than were the results of medical treatment and roentgen therapy.

Dr. Theodore Cornbleet, Chicago: I have been studying the excretion of the halogens in sweat, particularly in cases of furunculosis and folliculitis, and I wish to mention one case of hydrosadenitis suppurativa I have studied. There was a curve of excretion distinctly different from that obtained in control cases. Aside from that, the amount of iodide in the unfiltered sweat was about seven or eight

times greater than that in the filtered sweat. In other words, in cases of this condition there probably occurs a combination of the iodides with the epithelium which does not take place normally. I do not mention this to imply that this accounts for hydrosadenitis suppurativa, but the abnormality merely seems to be a peculiarity associated with the condition.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I think it is well to emphasize that if this condition is treated at all it should be treated radically from the beginning. If roentgen therapy is used large doses of irradiation should be employed, and if surgical treatment is resorted to, the lesions should be removed thoroughly and the area grafted. Treatment is difficult because of the peculiarities of the sites that are usually affected.

MULTIPLE CUTANEOUS GUMMAS RESISTANT TO TREATMENT; FIXED ARSENICAL ERUPTION.

Mr. A. LaB., a laborer aged 34, states that he resided in South America from 1922 to 1926. He had malaria there in 1923 and had a chancre in 1926. According to his statement he did not have secondary syphilis. In 1926 the Wassermann reaction of the blood was positive. In December 1935 the patient had diarrhea which lasted from two to three weeks. Previous treatment, which he received elsewhere, was as follows: from 1926 to May 1936 he was given thirty injections of neoarsphenamine and twenty-six injections of a bismuth preparation. From May to July 1936 he received twenty-six injections of fuadin and three injections of antimony and potassium tartrate. In July 1936 three roentgen and radium treatments to the ulcers were given.

In January 1936 a painful ulcer developed in the right scapular region, and in March 1936 an ulcer of the right knee appeared. During the past month smaller ulcers have appeared on the wrists, thighs, neck and chest.

The patient is well developed and does not appear acutely ill. His present weight is 141 pounds (64 Kg.); his usual weight, 180 pounds (81.7 Kg.). In the right infrascapular region there is a large ovoid ulcer, about 12 by 5 cm. The base is irregular and covered with necrotic slough. The edges are undermined, and the upper border is arciform. Numerous symmetrically distributed coin-sized ulcers are located on the wrists, on the lower portion of the legs, on the chest and on the back. These are more superficial and present firm elevated indurated borders with a clean granulating base. On the back, shoulders and upper portions of the arms are numerous bluish black pigmented lesions.

The Hinton test gave a positive reaction, the Kline, the Kahn and the Wassermann test each gave a 4 plus reaction. Urinalysis and the Frei test gave negative results. Roentgenograms of the chest showed no abnormalities. The blood and urine contained no bromides. Examination of the blood showed 4,820,000 erythrocytes, 8,000 leukocytes and 75 per cent hemoglobin. The differential blood cell count as well as smears and culture gave negative results.

Biopsy revealed changes consistent with the diagnosis of syphilis, including obliterative changes in the blood vessels and some plasma cell infiltrate.

Treatment at the Mayo Clinic during the past three weeks has consisted of symptomatic local measures, sulfur baths, local application of anesthetic ointments, specific treatment for syphilis and nonspecific fever therapy with typhoid vaccine. The patient's general health has improved; he has gained 5 pounds (2.3 Kg.), and there has been progressive healing of the ulcers.

DISCUSSION

DR. OLIVER S. ORMSBY, Chicago: This case presents features characteristic of pityriasis rubra pilaris. There are keratotic lesions on the fingers and trunk, a palmar keratoderma and seborrhea of the scalp. The histologic picture is quite typical of that disorder.

PSORIASIS; PSORIATIC ARTHRITIS.

Mrs. M. L., a housewife aged 42, states that her psoriasis began when she was 6 years old and has persisted for thirty-six years. Arthritis appeared in the left knee when she was 32 and has persisted for ten years. During the past four years the terminal joints of the fingers and toes hvae progressively become involved. There is a definite history that flare-ups of the cutaneous condition are associated with the involvement of the joints. Until the past four months the psoriasis has been kept under control with chrysarobin and solution of potassium arsenite. The patient states that the ingestion of fatty foods, such as bacon, increases the pruritus and that the psoriasis became more generalized recently when she gained weight. Three pregnancies have had no apparent effect on the psoriasis.

The patient weighs 203 pounds (92.1 Kg.). Superficial plaques of psoriasis are distributed chiefly over the extremities. Changes in the nails have been associated with the psoriasis. Physical examination gave essentially negative results except for obesity and arthropathy. There are typical swelling and deformity of the terminal joints of the fingers.

Examination of the blood and urine and flocculation tests gave negative results. The uric acid content of the blood was 5.6 mg. per hundred cubic centimeters. The urea content was normal; the cholesterol content was 231 mg.; the lecithin content, 348 mg.; the fatty acid content, 367 mg., and the lipoid content, 598 mg., per hundred cubic centimeters of blood; the sedimentation rate was 41 mm. in one hour. All these figures represent the upper limits of normal.

Treatment has consisted of a rigid reducing diet, administration of crude coal tar (2 per cent), ultraviolet irradiation, autoserum therapy, physiotherapy, contrast baths and nonspecific fever therapy with typhoid vaccine.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: This is one of a number of cases of the type of arthritis considered to be part of the psoriasis syndrome. The involvement of the terminal phalanges of the hands and feet is characteristic. Dr. Hench is convinced that whatever measures are used for the control of the arthritis fail unless the psoriasis is brought under control. For that reason patients with this condition are treated for psoriasis with various physiotherapeutic procedures as well as with application of the usual crude coal tar ointment and ultraviolet irradiation. In some cases the disturbance in the joints becomes so severe that surgical intervention is necessary.

HERPES GESTATIONIS.

Mrs. H. P. J., an American housewife aged 31, states that she had recurrent urticaria as a child. The first cutaneous disturbance began in July 1934, when she was in the seventh month of her first pregnancy. An erythematous vesicular eruption appeared about the umbilicus, groin, thighs and back. The eruption was definitely symmetrical, and burning rather than pruritus was the predominant symptom. While the patient was in the hospital new vesicular lesions developed in groups. These lesions were of the erythema multiforme type, and many of them were urticarial. In September 1934 she was delivered spontaneously of a stillborn macerated male fetus. Immediately after that a few new lesions appeared on the skin, but within a short time practically all the lesions disappeared. In June 1936, when the patient was in the third month of her second pregnancy, a recurrence of the vesicular eruption developed. Continuation of the pregnancy was considered unsafe because of the rapid spread of the cutaneous lesions, and the uterus was emptied on June 17. Recovery was uneventful. Since the operation there has been continued involution of the lesions with a few exacerbations, but on the whole there has been steady improvement.

Examination of the blood showed a marked eosinophilia, the percentage of eosinophils being from 28 to 51, during the acute phases of the vesicular eruption. Serum potential tests made on June 13, 1936, gave a positive reaction with erythema multiforme antigen. Cultures of the blood and of material from the

nasopharynx were positive for the erythema multiforme type of streptococcus (Welsh). On Aug. 25, 1934, the basal metabolic rate was normal. The blood showed a moderate secondary anemia.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: I think it is important that this woman's pregnancy was interrupted because of this condition, and I think that the intervention was wise. My co-workers and I observed a case in which a pregnant woman went through a great deal of trouble, the pruritus persisting after the birth of the child. I think pregnancy should be interrupted in cases of such a severe condition.

DR. PAUL A. O'LEARY, Rochester, Minn.: My co-workers and I saw this woman during her first pregnancy in 1934, when she exhibited a severe generalized papulovesicular eruption which persisted until she was delivered of a dead fetus. She became pregnant again this spring; at about the sixth week of the pregnancy papulovesicular lesions developed about the finger-nails, and shortly afterward bullous lesions appeared on the forearms. Day by day the cutaneous condition became worse, and it was deemed necessary to perform a therapeutic abortion. At the same time a hysterectomy was performed for other reasons, and the involution of the cutaneous lesions has been going on slowly. I wish to call attention to the fact that the involution of the cutaneous lesions was more rapid in the first than in the second attack.

DR. OLIVER S. ORMSBY, Chicago: In the case of a patient with a serious attack of herpes gestationis my co-workers and I used intravenous injections of blood serum obtained from women in the same stage of pregnancy as the patient, which in our case was the seventh month. Three injections of 20 cc. of serum were given at intervals of five days. Remarkable results were obtained after other measures had failed.

DR. H. E. MICHELSON, Minneapolis: In our case my co-workers and I used blood from several pregnant women in all stages of pregnancy but obtained no results.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: The first pregnancy in this case resulted in a stillbirth. At that time there was an eosinophilia, the percentage of eosinophils being 51.

TUBERCULOSIS CUTIS INDURATIVA (IDIOPATHIC ATROPHY? POIKILODERMA?)

Mr. C. F., a painter aged 37, states that in 1921 the skin of his trunk and extremities became dry, scaling, pruritic and slightly reddened. The redness increased until 1931, when it became stationary except for the fact that some improvement occurred in the summer. The patient also had alopecia areata (?) for one month at this time. In 1926 an abscess developed in the neck, draining above the sternum and left clavicle. The neck became freckled and has remained so. A tuberculous gland was removed from the left supraclavicular area in 1934. In 1928 an abscess which had developed in the left groin was incised and discharged considerable pus but healed rapidly. In 1934 a soft painless swelling developed in the left lumbar region. The left ankle also swelled, and the swelling was diagnosed as "cold abscess." There was red discoloration of both legs, the pigmentation later becoming brown and increasing to diffuse brownness. Both legs swelled, and an ulcer appeared on the left leg. This healed when the patient was confined to bed.

The left leg is larger than the right. Swelling is increased by standing and decreased by rest in bed. In 1935 a second ulceration of the left leg followed mild trauma. This again healed as a result of rest in bed. In February 1936 there was puffy swelling of the medial aspects of both thighs. The general health has been good, but there has been some weakness during the past few months. The patient worked at a blast furnace in a foundry in 1928, continuing to do that type of work until 1931. He is now a painter.

The skin shows superficial atrophy associated with slight dusky brown erythema and a mild ichthyosiform type of scaling. The involvement is diffuse and generalized, but the face, scalp, palms and soles are not involved. The eruption is accentuated on the extensor surfaces of the legs and arms and in a bandlike area across the abdomen just above the umbilicus. There is a band of dark drown discrete macular pigmentation with atrophy, 2 or 3 inches (5 or 7.6 cm) wide around the base of the neck; the posterior portion is darker. Scars of abscesses and incisions are seen in the jugular fossa and in the left supraclavicular region. In the left lumbar region is a firm deep elastic nontender swelling associated with looseness and purplish brown discoloration of the overlying skin. The adjacent lumbar portion of the spine is prominent. In the left subinguinal region is a painless matted mass of glands with loose overlying skin. Varicosities of grade II are present on both legs. There are scars of old ulcerations on the left thigh and leg; some are grouped and some are arciform. The palms and soles are mildly ichthyotic; the nails are brittle. A small mucocele is present on the right side of the lower lip.

Examination of the blood showed 4,790,000 erythrocytes, 5,500 leukocytes and 95 per cent hemoglobin. The differential blood cell count gave the following results: polymorphonuclears, 65 per cent; lymphocytes, 21.5 per cent; monocytes, 8.0 per cent; eosinophils, 5.5 per cent.

A roentgenogram of the chest showed no abnormalities; that of the spine showed a narrowed lumbosacral intervertebral space, slight marginal thickening of both sacro-iliac joints and swelling of the soft tissue of the medial aspect of the left thigh, the swelling being apparently in the subcutaneous tissue.

Biopsy of a specimen from the arm revealed the histologic picture of sarcoid (tuberculosis cutis indurativa); that of material from the neck showed histologic changes consistent with an idiopathic atrophy or poikiloderma (Jacobi).

DISCUSSION

DR. OLIVER S. ORMSBY, Chicago: This patient presents patches like those of poikiloderma of the Jacobi type on the trunk, but these areas lack the pigmentation and telangiectasia seen in true poikiloderma. On the neck the so-called Civatte type of poikiloderma, which now is considered identical with Riehl's melanosis, is present. On the trunk are large areas of skin which show the wrinkling and scaling atrophy such as are observed in cases of acrodermatitis atrophicans or idiopathic atrophy. The deeper lesions I cannot explain. I should classify the condition as idiopathic atrophy.

DR. S. W. BECKER, Chicago: I am inclined to agree with Dr. Ormsby that the condition is an idiopathic atrophy. There is some melanosis. About the neck there is a little change that resembles roentgen atrophy, but there is little if any telangiectasia. I have no further diagnosis to offer.

DR. H. E. MICHELSON, Minneapolis: It seems to me that the most important thing in this case is a large plaque on the arm, a section of which shows sarcoid. The atrophic process may be the result of the sarcoid infiltration. Leprosy, of course, will have to be ruled out.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Histologic examination of the lesion on the arm showed the picture of sarcoid, but that of the lesion on the neck showed a picture suggestive of poikiloderma or idiopathic atrophy. In the old literature there are reported cases of pityriasis rubra of Hebra in which the condition was shown to be of tuberculous etiology. It is possible that this patient may have had a true exfoliative dermatitis with a resulting erythroderma and atrophy. In most of the former cases in which the condition was diagnosed as Hebra's disease it has proved to be lymphoblastoma, but in two or three of the older cases in the literature there was a definite tuberculous architecture in the skin. I believe that the disease in this case fits in this group.

NOTE.—Biopsy of material from the mass in the groin also showed the histologic picture of tuberculosis together with foreign body giant cells.

MANHATTAN DERMATOLOGIC SOCIETY

MIHRAN B. PAROUNAGIAN, M.D., *Secretary*

March 10, 1936

PAUL E. BECHET, M.D., *Chairman*

A CASE FOR DIAGNOSIS (SYPHILIS?) IN THE THIRD GENERATION. Presented by DR. FRED WISE.

P. L., aged 3½ years, a well developed and well nourished girl, in the care of Dr. Rein and Dr. Shostac, presents no clinical stigmas of congenital syphilis. The reaction of her blood was strongly positive on repeated Kline, Kahn and Wassermann tests. Her mother, aged 24, presents no clinical evidence of syphilis; Kline, Kahn and Wassermann tests of her blood gave strongly positive reactions. The patient's father shows no clinical or serologic evidence of syphilis. Two maternal aunts, aged 30 and 26, respectively, had negative serologic reactions, while two maternal uncles, aged 21 and 17, respectively, had positive serologic reactions. One maternal uncle (L. C.), aged 15, shows no clinical or serologic evidence of the disease. The patient's maternal grandmother, aged 54, first reported to her physician in 1921 complaining of nervousness. She received at that time injections into the arm and into the hip for one year. These injections were received just before the birth of her youngest son, L. C., who shows no evidence of syphilis. Tests of the grandmother's blood were repeated in November 1935 and gave positive reactions. The patient's maternal grandfather, F. C., had a chancre about twenty-five years ago and reported to his physician, who gave him three injections of arsphenamine. It is not known whether he received any other antisyphilitic treatment. He died at the age of 37 of an accident.

DISCUSSION

DR. GEORGE M. MACKEE: This is an interesting observation. Probably the child has third generation syphilis, but I do not feel that it is a proved case. The possibility of acquired syphilis in the mother has not been definitely ruled out; in fact I do not know of any way in which a case like this can be definitely established.

DR. J. FRANK FRASER: I agree with Dr. MacKee that it cannot be proved that the disease was transmitted to the third generation. Syphilis is not a hereditary disease in the sense that it is transmitted through the chromosomes. Congenital syphilis is contracted in utero, spirochetes from the mother's blood gaining entrance to the fetal placenta.

DR. MAX SCHEER: I agree with Dr. MacKee and Dr. Fraser that proof of syphilis in the third generation is lacking. The grandmother may have been infected after the birth of the mother. The evidence for syphilis in the third generation would be much stronger if the mother showed some stigma of congenital syphilis. It is also possible for a person with congenital syphilis to acquire syphilis later on.

DR. LUDWIG OULMANN: While I agree with Dr. MacKee that it is hard to prove cases of this kind to be instances of syphilis in the third generation, the lack of any stigma other than the positive reaction of the mother's and of the child's blood together with the fact that the child's father never showed any symptoms of the disease makes the diagnosis of syphilis in the third generation probable.

PUSTULAR PSORIASIS. Presented by DR. ISADORE ROSEN.

S. C., a man aged 35, was first seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, on March 2, 1936, exhibiting an eruption on the hands, feet, elbows and scalp of three months' duration. There

is no family history of psoriasis. On the soles, on the dorsal aspect of the heel and on several of the toes there are sharply defined coin-sized patches consisting of minute intradermal vesicles and pustules. Several lesions on the feet showed desquamation. There are changes in the toe-nails. There is some maceration of the skin between the toes. Similar lesions are present on the hands, especially on the thenar areas of the palms. On the dorsal aspect of the elbows there are coin-sized patches of micaceous scales. The scalp along the frontal hair line also shows scaling. These lesions itch slightly. One examination for fungi was reported to have given negative results.

DISCUSSION

DR. FRED WISE: I agree with the diagnosis.

DR. EDWARD R. MALONEY: I should make a clinical diagnosis of either pustular psoriasis or psoriasis with pustules. Recently I made a diagnosis of pustular psoriasis in what was almost a classic case. A Wassermann test was reported to show a 4 plus reaction, and after a few weeks of antisyphilitic treatment the eruption disappeared. Hereafter when I have a patient with a disorder that looks like pustular psoriasis I shall have a Wassermann test made.

DR. GEORGE M. MACKEE: One must be careful in making a diagnosis of pustular psoriasis, as the disorder can be so easily confused with dermatophytosis, dermatophytid and other conditions. A few years ago I was under the impression that there were never any vesicles in pustular psoriasis; now I believe that vesicles may precede the pustules.

Dr. Maloney's report is interesting, but I should not be willing to make a diagnosis of syphilis because an eruption disappeared as a result of arsenic therapy. Many of the members may recall that years ago arsenic was a favorite remedy for psoriasis, and at times the result of arsenic therapy appeared to be spectacular.

In Dr. Rosen's case there cannot, of course, be any question of syphilis. The biopsy showed a picture that is usually found in pustular psoriasis of the soles. In other words, a picture that resembles eczema more than psoriasis. I think that the clinical evidence in this case is in favor of pustular psoriasis, but at present I cannot eliminate the possibility of eczema due to fungi or their products.

DR. PAUL E. BECHET: The lesions on the elbow are rather nondescript and are certainly not characteristic of psoriasis. They could well have been caused by pressure or friction. The eruption on the feet resembles a typical dermatophytosis. Negative results of one or two tests for fungi prove nothing, and only further negative results of examinations would cause me to abandon the diagnosis of ringworm; even then I should prefer the diagnosis of recalcitrant pustular dermatosis of the feet, as descibed by Andrews, to that of pustular psoriasis.

SECONDARY SYPHILIS. Presented by DR. ISADORE ROSEN.

G. B., a woman aged 30, American, a housewife, was first seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, on March 6, 1936, exhibiting an eruption on the face of two months' duration.

There is a red scaly infiltrated and serpiginous eruption, which is especially marked on the forehead. On the dorsal aspect of the neck there are scattered fleshy papular lesions with some scaling. There is a partial alopecia of the eyebrows. On the backs of the hands and around the wrists is a well defined brownish red eruption. There is no itching.

A vaginal and anal examination were not made. There was a general adenopathy. The patient has received one injection of a bismuth preparation. Wassermann and Kahn tests will be made.

W. B., the patient's husband, American, a carpenter, was seen at the clinic on the same day, exhibiting an eruption on the upper extremities, chest and back of five months' duration.

He presents a general papular and macular eruption accompanied by a generalized lymphadenopathy. The lesions vary from red to copper color. There are no palmar or plantar lesions. The occipital regions present marked alopecia, and on the posterior surface on the penis there is a pea-sized hard slightly ulcerated papule. He has received one injection of a bismuth preparation.

The results of the Wassermann and Kahn tests have not been reported.

DISCUSSION

DR. MIHRAN B. PAROUNAGIAN: In my opinion the wife was infected first. Her lesions are older. She has marked syphilitic alopecia, whereas the husband has a marked early roseola.

DR. GEORGE M. MACKEE: One can learn a great deal about clinical dermatology by observing atypical lesions in typical eruptions. In this case if the patient had only the eruption on the face one might make a diagnosis of lupus erythematosus. The eruption in that area shows atrophy, a lighter color than is usually seen in syphilis and adherent scales. I agree with the diagnosis as presented.

DR. LUDWIG OULMANN: The woman has seborrhea of the scalp and forehead, which causes the change of color of the syphilitic lesions of that region.

REPORT ON A CASE PREVIOUSLY PRESENTED.

Dr. J. Frank Fraser reported on a case which Dr. Andrews had presented at the January meeting with a questioned diagnosis of granuloma annulare resembling epithelioma (ARCH. DERMAT. & SYPH. **34**:724 [Oct.] 1936). Further microscopic study proved the lesion to be basal cell epithelioma.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

FRANK C. COMBES, M.D., *Secretary*

May 20, 1936

MAX SCHEER, M.D., *Chairman*

A CASE FOR DIAGNOSIS. Presented by DR. B. LAPOWSKI and DR. ABRAHAM WALZER.

H. G., a man aged 34, is presented from the Good Samaritan Dispensary and Hospital. He exhibits an eruption involving the face, trunk and extremities, of three years' duration. There is nothing of importance in the past history. The eruption began three years ago as a penny-sized papulovesicular patch on the left thigh. Eight weeks later, when the patient was first seen, the eruption had already spread to involve the entire body in large papulovesicular patches. He attended the clinic for a short time only. During the past three years he has received in various institutions many intravenous and intracutaneous injections, roentgen and ultraviolet irradiation and various local applications, but he has had no relief. His skin has been tested for hypersensitivity, and he has been given various internal medications and has followed various diets. Numerous examinations of the blood and urine and chemical examinations of the blood have been made. During this time the eruption has changed from a papulovesicular to a lichenoid type, and at another time it was almost like a universal neurodermatitis. At times he shows a generalized exfoliative dermatitis.

Tonight the eruption involves the entire trunk, the face and the extremities. It consists of erythematous papules and patches, varying in size from that of a pinhead or a pea to that of a dime. The papules are flat and not sharply outlined,

and their degree of elevation varies. The papular lesions usually occur singly and are lichenoid. The patches, which are combined papular lesions, usually occur in groups, lines and irregular formations. Some of them show a smooth surface with exaggerated skin markings, while on others the surface is irregular, rough and covered with more or less adherent, dry scales which suggest psoriasis. The skin between the lesions is normal. Pruritus is severe, as evidenced by the presence of many excoriated lesions, many of which are covered with hemorrhagic crusts. All the external glands are enlarged and hard. Physical examination gave negative results.

Laboratory tests, including blood counts, gave negative results. The Wassermann reaction was negative. Histologic examination showed a definite exudative process like that seen in psoriasis but with too many plasma cells. No diagnosis can be based on the histologic examination.

DISCUSSION

DR. MARION B. SULZBERGER: I have been particularly interested in a group of conditions which, I think, cause a picture similar to that exhibited by this patient. I believe that it is impossible to classify this disease accurately as any known dermatologic entity heretofore described. I think this case, like many others presented for diagnosis, requires much further investigation before one can have even an inkling as to the exact nature of the disease, its etiology and its pathogenesis, but it seems to me that even today this condition may be considered to represent a dermatosis that has a characteristic picture. In my experience this dermatosis is predominantly seen in males. There are circumscribed eczematous plaques, which at certain times become infiltrated and then suggest lymphoblastoma or even the premycotic stage of mycosis fungoides. At other times the eruption is polymorphous, both eczematous and urticarial elements being present, and resembles atypical forms of Duhring's disease, and at still other times there is discrete follicular and diffuse lichenification. In the cases of this condition which I have observed there have been persistent penile lesions, and this seems to be an almost constant and diagnostic finding. Some cases may have occurred in females, but I do not think that all the characteristics of the dermatosis were present in any females I have observed. One of the most distinctive characteristics of this dermatosis is that it has been refractory to every form of therapy. It has not responded to arsenic or roentgen radiation; in short, any known therapeutic measures which usually bring at least some alleviation in most eczematous dermatoses, in Duhring's disease and in leukotic dyscrasias with cutaneous manifestations have been useless. I do not know whether this dermatitis will prove to be the forerunner of some other condition or whether any other known dermatosis will supervene. In these cases I have observed in the past four years no other known dermatosis has supervened. I think it is extremely unlikely that the condition will turn out to represent early stages of a so-called lymphoblastoma; the relatively common occurrence of the condition, its refractoriness to roentgen therapy and the fact that not one patient with the malady has as yet shown a characteristic picture of a leukotic dyscrasia—all these factors speak definitely against that supposition.

The only thing I have observed to be of benefit has been a change of environment. Most of the patients do well when they are hospitalized and show a recurrence promptly when they return home. Most cutaneous tests, including patch tests, ordinary scratch tests and intracutaneous tests with trichophytin and oidiomycin have given negative results in cases of this disease. One seems to be up against a stone wall as regards both etiology and adequate therapy.

DR. GEORGE C. ANDREWS: I agree in great part with what Dr. Sulzberger has said. In this connection I should like to recall the case which Dr. Kaufman presented before this section in February 1935 (ARCH. DERMAT. & SYPH. **32**:962 [Dec.] 1935). The patient, who was from the Vanderbilt Clinic, had a similar eruption. He had been treated in Greece, at the Vanderbilt Clinic and at the

Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, I believe. About five biopsies and innumerable blood counts had been made. The patient presented a generalized, somewhat infiltrated, patchy eruption, similar to that exhibited by the patient of Drs. Lapowski and Walzer, although his skin was darker and the patches were therefore darker and not as bright red. My co-workers and I have observed that man at the Vanderbilt Clinic for four years. To our great surprise his condition did not respond to roentgen radiation. He has received arsenic and calcium medication and injections of arsphenamine and has been subjected to all kinds of tests and treatments, and the eruption is unchanged. He has the same glandular enlargement as that displayed by this patient. We have never come to a definite conclusion or diagnosis of his condition.

DR. ADOLPH ROSTENBERG: At the last meeting my son and I presented a patient with like manifestations. I wish to report that we have given that man injections of typhoid vaccine. Subjectively, he is much better and feels somewhat relieved. I think fever therapy may prove of value in treatment of this disease.

DR. ISADORE ROSEN: I have discussed this group of conditions for the past three years, and there is little to add. I agree that the disease responds to hyperpyrexia, but as a rule the eruption has a tendency to recur after the patient is discharged from the hospital.

I doubt much that this patient's condition has been stationary for the past three years. Patients with this disease usually show improvement clinically, often without having received treatment, while they are in the hospital. The condition has been thoroughly studied from every angle. Some of the patients have been in the hospital for from four to six months at a time, and they have been examined by internists, rhinologists, gastro-enterologists, endocrinologists and allergists. Differential blood counts and numerous biopsies in the various stages of evolution of the eruption have been made, but no positive information has been obtained. In view of the negative findings my co-workers and I have come to the conclusion that there must be some disturbance in the metabolism or physiology of the skin itself. Dr. Rosenfeld, Dr. Krasnow and I (ARCH. DERMAT. & SYPH. **33**:518 [March] 1936) reported studies on the lactic acid content of the sweat. We found a marked increase in patients with this condition during the first few treatments with hyperpyrexia and a gradual return to normal as improvement occurred.

DR. ABRAHAM WALZER: We are fortunate in having observed this patient almost from the onset of the disease, and we have been able to see the various changes in the eruption. We saw him when he had the lesions about six or seven weeks. He then presented what we considered a papulovesicular eruption, which was more or less localized to various parts of the body. This disappeared. We saw him a number of times later with different types of eruptions. At one time he appeared with a generalized markedly pruritic papular eruption. At other times he presented a generalized dermatitis exfoliativa, probably due to overtreatment received in various institutions. At one time he had what looked like a generalized neurodermatitis. The present eruption has existed for about a year.

As far as further investigation in this case is concerned, we cannot imagine what else we could do in our present state of knowledge regarding this type of disease. Dr. Rosen's suggestion as to investigations into the physiology of the skin of this patient is interesting, but it is difficult to conceive how such a problem could be attacked and what the patient would gain by these investigations. All the work that has been done in many cases of similar eruptions has up to the present time been of no value.

As to the various suggestions of methods of therapy, they are all interesting, but we have seen this patient improve much with applications of the simplest remedies, such as petrolatum and calamine lotion. At other times his condition has cleared up almost completely after a rest in the country for a week or two, and then without any apparent reason, another attack has suddenly occurred. At present I think one has to admit little is known about this condition. The outlook is not promising.

A Case for Diagnosis (Lichen Atrophicus?) Presented by Dr. B. Lapowski and Dr. Abraham Walzer.

H. S., a man aged 40, is presented from the Good Samaritan Dispensary and Hospital because of an eruption of sixteen years' duration involving the lower portion of the legs, the ankles and the dorsa of the first, second and third toes of the right foot. The only fact of importance in the family history is that a younger brother has had a similar eruption on the legs for four years. The lesions appeared about sixteen years ago on the toes of the right foot and then gradually extended to the other locations. The patient has been treated in other institutions with subcutaneous and intracutaneous injections and roentgen irradiation, but no improvement has resulted. He has been under observation at the clinic of the Good Samaritan Dispensary and Hospital since August 1935.

The process apparently begins as an erythematous point which disappears under pressure. These erythematous points increase in size and number, become a little darker, and then, on pressure with the diascope, show points of pigmentation. They further increase in size, becoming almost dime-sized; the centers become depressed, whitish, scaly and atrophic, but the borders remain red, later becoming brown. During the entire development there is apparently no elevation of the lesion. It seems to be in and under the skin. Many of these lesions unite to form irregular and serpiginous patches. In some instances the process has not progressed to atrophy but has apparently ended in brown pigmentations with an erythematous border.

Physical examination, including roentgen examination of the chest, showed no tuberculosis. Neurologic examination showed a progressive muscular atrophy of the Charcot-Marie type which appeared after the cutaneous lesions and is of about six or seven years' duration. The laboratory examinations, including biopsy, blood count, sedimentation test, tuberculin test and urinalysis, all gave negative results. The Wassermann reaction was negative.

DISCUSSION

Dr. E. William Abramowitz: The eruption looks to me like Majocchi's purpura annularis telangiectodes.

Dr. Abraham Walzer: My co-workers and I considered a number of diagnoses, but only one was suggested tonight, that of Majocchi's disease. I am not at all satisfied with the diagnosis of lichen atrophicus. There were never any real lichen or even lichenoid papules during the entire time the patient has been under observation. What he shows are tiny erythematous puncta, which appear singly and in groups and are scattered around the entire lesion. On pressure with the diascope tiny red or brown points can be seen.

Majocchi's disease is an acute disease; an attack lasts a few months, and there may be recurrences. In this patient the lesions have persisted for over ten years. The atrophy in Majocchi's disease is faint, while in this case it is prominent. The histologic picture is also against Majocchi's disease. The slides were examined by Dr. Satenstein. They show no endarteritis or aneurysmal sacculation whatever. The chief characteristics are telangiectasis, atrophy of the cutis and absence of tissue reaction.

This patient was treated at the Vanderbilt Clinic in 1926. A report received from the clinic stated that the clinical diagnosis at that time was lichen atrophicus, but the biopsy did not show that condition.

Leukoplakia. Presented by Dr. Oscar L. Levin.

M. A., a man aged 56, an Egyptian Arab, is presented from the Beth Israel Hospital. About one and a half years ago the patient noticed the appearance on his tongue of a number of white sores which did not bleed and were painless. Several months later the inner surface of his lower lip became involved. He remembers that he had an ulcer on his penis and also a gonorrheal infection about twenty-five years ago.

The blood pressure was 210 systolic and 110 diastolic; except for that observation the physical examination gave negative results.

The greater part of the internal surface of the lower lip presents an elevated chalky white verrucous lesion with sharply demarcated borders and traversed by fissures. The mucous membrane of the cheeks shows a diffuse grayish white plaque formation. The dorsum of the tongue from the tip backward presents atrophy and glossiness and is dotted with pea-sized whitish islets of leukokeratotic tissue. On the left margin of the tongue a pea-sized verrucous growth was removed for biopsy.

Urinalysis gave negative results. The blood count showed 4,080,000 red cells and 12,100 white cells. The differential count gave normal results. The Wassermann reaction of the blood was 4 plus. The spinal fluid was normal. Cultures for fungi gave negative results. The report on the biopsy from the lesion on the lip was chronic leukoplakia with thick horny layers.

From June to September 1935 the patient received six injections of neoarsphenamine and seven of mild mercurous chloride, but no improvement of the oral lesions occurred. These injections were given at the Good Samaritan Dispensary and Hospital. At the Beth Israel Hospital, since Feb. 28, 1936, he has received nine injections of arsphenamine and nine of a bismuth preparation. No improvement has been noted.

DISCUSSION

DR. ISADORE ROSEN: I feel that the administration of arsenic is a dangerous procedure in cases of this condition. I have seen rapid epithelial proliferation occur after intravenous arsenical therapy. I am of the opinion that arsenic is contraindicated in all cases of leukoplakia, and I treat that disease with the milder remedies, such as bismuth or mercury with potassium iodide.

DR. GEORGE C. ANDREWS: I think that there is imminent danger of cancer of the tongue developing even if the patient is not treated with arsphenamine or mercury. In fact, he has a verrucous proliferation on the tongue now. In spite of the fact that the biopsy showed that it was a connective tissue growth, I feel that if tissue from some other area were examined microscopically it might show epithelioma. The outlook for this patient is bad, regardless of treatment. If lesions of a fungating or proliferating type arise on the tongue, they should be excised because excision may be a prophylactic measure against the spread of cancer if performed early enough. The leukoplakia of the lip and inside the mouth can be treated easily by plastic surgery now. There is enough mucous membrane on the inside of the lip to cover the area of leukokeratosis, and the lesions in the buccal mucosa can be treated similarly. My co-workers and I use excision and pulling over of healthy mucous membrane as a routine; and it is a simple surgical procedure.

DR. A. BENSON CANNON: I do not consider this man's condition as grave as has been pictured. I believe that his leukoplakia of the mucous membranes of the mouth and tongue and his leukokeratosis of the lip are manifestations of syphilis. I see no evidence of an epithelioma. I think that the man should have thorough antisyphilitic treatment, and I agree with Dr. Rosen that for the present the treatment should consist of administration of bismuth and potassium iodide and of thorough lubrication of the parts several times a day with olive oil. I also suggest that the patient stop smoking. If these recommendations are followed I believe that in from six to eight months the condition will probably clear up except for the leukokeratosis of the lip, which will probably have to be removed with the desiccating needle. I treated a patient with a condition that was exactly like the one exhibited by this patient, and the results were such as I have predicted. About seven years have elapsed since I first treated the patient, and he has remained well. The erosion on the corner of the mouth and the one on the tongue I consider to be syphilitic.

DR. CHARLES WOLF: From the clinical aspect the disease is advanced leukoplakia. From the pathologic standpoint the lesions probably would show early malignant changes. The question is what to do for the patient. I advocate immediate treatment with radium needles used interstitially.

DR. FRED WISE: I palpated the lesion and detected no infiltration at the base. The lesion on the lip is superficial and on histologic examination will probably show no infiltration of the deep structures. Of course, no one can say that there is no malignant degeneration at present, but I do not think that there is any. I think it is erroneous to think that there is immediate danger of death or even remote danger of serious results. My impression is as follows: If the patient stops smoking the tongue and buccal mucous membrane will probably get well, but the lip will not because it shows a proliferative leukokeratosis which does not get well when a patient stops smoking, in contradistinction to the flat lesions which do get well. I think it is a simple matter. I should treat the lesion with monopolar electrodesiccation and avoid plastic operation or other more radical measures. I think that as long as there are no metastases this simple form of treatment will be efficacious.

DR. JESSE A. TOLMACH: The lesion on the lip is superficial, and the histologic study did not reveal any evidence of malignant degeneration. In view of the fact that the lesion is precancerous, it certainly appears logical to remove it in its present benign stage. I shall refer the patient to the surgical department for excision.

A CASE FOR DIAGNOSIS (TINEA AMIANTACEA OF ALIBERT?). Presented by DR. HERMANN FEIT.

J. Z., a youth aged 17, born in the United States, was told by some friends when he was swimming in an indoor pool about three weeks ago that he had a bald spot on his scalp. The patient was absolutely unaware of this fact, as he had no subjective sensations.

The occipital region of the scalp shows a bald spot, about the size of a 50 cent piece, in which there are few hairs but no broken-off hairs. The base is reddened, mortar-like in color and scaling.

Microscopic examination showed no fungi.

DISCUSSION

DR. GEORGE M. LEWIS: My diagnosis is tinea capitis. The fluorescence test should be positive, and culture should make it possible to determine the causative fungus. There is not sufficient clinical evidence to justify the diagnosis of either tinea amiantacea or seborrheic dermatitis.

DR. CHARLES WOLF: I suggest the diagnosis of trichotillomania.

DR. HERMANN FEIT: So-called tinea amiantacea has been described by Alibert. The characteristic features are (1) alopecia; (2) falling off of the hair in toto but no breaking off. This case is a good example of that disease. Dr. Benham has examined the patient carefully and cannot find any tinea. The name is misleading. Darier considered tinea amiantacea a form of dry eczema. I wonder whether any one has seen a dry eczema causing a bald spot of this kind with such sharp outlines. The lesion corresponds to the description given by Alibert. Dr. Hopkins also agrees with this.

PAPULONECROTIC TUBERCULIDE IN A PATIENT WITH PSORIASIS. Presented by DR. HERMANN FEIT.

S. M., a man aged 29, from the New York Society for the Relief of the Ruptured and Crippled, has an eruption of five weeks' duration. He has typical psoriasis on the elbows and knees, and along the course of the large veins of the leg he exhibits subcutaneous nodules of different sizes which break down and leave pigmented scars. The Wassermann and the Kline tests were negative. A salt-free diet, halibut liver oil and generalized irradiation with the air-cooled quartz mercury vapor arc lamp have been advised.

DISCUSSION

DR. MARION B. SULZBERGER: I think it would be difficult to decide whether the disease is actually a papulonecrotic tuberculid, the reasons for doubt being as follows: (1) There are no demonstrations of tubercle bacilli; (2) there are no histologic changes characteristic of the tuberculid; (3) there is no suggestion of the possibly tuberculous nature of the condition on the basis of an altered tuberculin immunology as shown by quantitative cutaneous tests; (4) the unilateral localization is much against that diagnosis; (5) the sex of the patient speaks somewhat against it, and (6) the appearance of the lesions is in no way typical of papulonecrotic tuberculid. The lesions exhibited by this patient are much larger and crusted, and there is no evidence of old lesions which have healed and left the typical round scars with depigmented centers and peripheral hyperpigmentation which one sees in papulonecrotic tuberculid. Therefore, I think further information is required before the diagnosis of papulonecrotic tuberculid can be accepted. Everything now known seems to speak not for but against that diagnosis. I should rather suggest the diagnosis of superficial pyoderma. Perhaps the disease is a superficial variety of ecthyma.

DR. MAX SCHEER: I suggest the diagnosis of ecthyma. I think that if the crust were removed a well of pus would probably be found underneath the crust.

DR. HERMANN FEIT: If the members had observed the patient a little longer they might have seen that these lesions are deep-seated nodules which follow the veins, break down and then heal, leaving scars and pigmentation. I must admit that I have made no search for tubercle bacilli, and I do no think that any one else has observed them in tuberculids. The diagnosis was made clinically, and the patient improved after treatment with ultraviolet radiation and a high vitamin diet. I have never seen ecthyma starting with deep nodules and always taking the same route, namely, following the veins. I consider the condition phlebitis of tuberculous origin, and I shall try to prove this assumption later.

DR. A. BENSON CANNON: I wonder whether Dr. Feit has considered the possibility of the lesions being due to a thrombosis of the varicose veins occurring when the veins were treated several months ago. The lesions are in direct line with the varicose veins, and the patient states that the nodules appeared at the sites where solution was injected into the veins.

DR. HENRY D. NILES: Dr. Cannon has just brought out the point I was going to make. The patient states that injections into varicose veins were made about a year ago. The location is interesting. The lesions are linear and follow the line of the vein which can be felt to be thrombosed underneath. There may have been a decreased resistance of the skin in that area which allowed the formation of an ecthyma. Another thing to consider is the possibility of bromoderma or iododerma, but no history of ingestion of bromides or iodides can be obtained. I cannot agree with the diagnosis of papulonecrotic tuberculid.

A CASE FOR DIAGNOSIS (LICHEN RUBER ACUMINATUS? DRUG ERUPTION?). Presented by DR. HERMANN FEIT.

M. P., a woman aged 45, born in the United States of German parents, had jaundice for about five months eight years ago but otherwise has never been ill. She is highly emotional and has an enlarged thyroid gland and a fine tremor of the hands. She states that she took large amounts of ex-lax. About six months ago she noticed an eruption on the abdomen which she attributed to contact with a rubber girdle. This eruption was itchy and consisted of purplish red blotches. It gradually spread upward and downward, being mostly confined to the trunk.

The distribution and configuration of this eruption suggest pityriasis rosea, but on closer inspection there is noted a follicular keratosis, especially over the lumbar region. In some places there is definite atrophy showing the oval outline of the former lesions which are now mostly replaced by pigmentation.

DISCUSSION

DR. EUGENE TRAUGOTT BERNSTEIN: The patient presents an eruption resembling pityriasis rosea, coincident with a papular eruption consisting of lesions from the size of a pinhead to that of a lentil resembling lichen spinulosus. On running the hand over the surface of the latter eruption one receives the impression of a nutmeg grater. The peculiar pigmentation of the sepia-brown lesions suggests lichen planus in a state of regression. The diagnosis, so far, is between pityriasis rosea and a lichen spinulosus-like toxic eruption, and lichen planus in a state of regression. Biopsy and further clinical observation are necessary to arrive at a final decision.

DR. FRED WISE: I think it can be said without fear of contradiction that the patient presents none of the lesions of lichen ruber acuminatus or pityriasis rubra pilaris. The hands are entirely free from lesions. She presents spinulous lesions, which are the most obvious ones, in connection with atrophic spots. I believe this eruption corresponds with the description of lichen spinulosus followed by atrophic spots as given in Jadassohn's *Handbuch*.

DR. E. WILLIAM ABRAMOWITZ: The annular lesions, the pigmentation and the shiny flat-topped papular lesions are rather characteristic of lichen planus. Lichen spinulosus is also present. The two types of lesions are sometimes found together.

DR. A. BENSON CANNON: I agree with Dr. Abramowitz that this case is one of lichen planus and lichen spinulosus.

DR. HERMANN FEIT: I think one can sum up the whole situation by saying that the disease is an atypical lichen planus, namely, a type having the accidental distribution of pityriasis rosea with lichen spinulosus.

TUBERCULOSIS COLLIQUATIVA. Presented by DR. B. LAPOWSKI and DR. ABRAHAM WALZER.

R. C., a woman aged 56, is presented from the Good Samaritan Dispensary and Hospital because of an eruption on the left leg of fifteen years' duration. Her husband died of pulmonary tuberculosis seven years after her marriage (twenty-seven years ago). Except for this the past history is unimportant. The condition began with a deep-seated nodule on the left leg above the ankle which softened and then ulcerated. It was treated locally and healed within about a year. For the past fourteen or fifteen years similar small nodules, which would ulcerate, have appeared on the same leg but have healed as a result of local treatment. About a year and a half ago a number of such ulcerations appeared, but this time they did not heal but rather increased in size and in number. The patient received all types of therapy, including roentgen irradiation and treatment with the air-cooled quartz mercury vapor arc in various institutions without any effect. When she first came to the Good Samaritan Dispensary and Hospital, in September 1935, she showed on the left leg a patch larger than the palm composed of many ulcerations arranged in a serpiginous formation.

In the central third of the left leg there is a cufflike area with a fairly sharp, advancing border composed of ulcerations. Within this area are numerous scattered superficial ulcerations from the size of a pea to that of a 25 cent piece with irregular and raised borders. The floors are dirty, moist and covered with whitish soft necrotic tissue. Posteriorly the ulcers are covered with crusts. Some of these ulcerations by their grouping and depth give the impression of gummas. Many ulcerations have appeared on the previously healed areas. Along the lower portion of the area anteriorly and also on the outer part is an irregular elevated rough scarlike area consisting of healed ulcerated lesions.

Physical examination and roentgen examinations of the chest show a suspicious involvement of the apex of the left lung. Examination of the blood, urinalysis and Wassermann tests all gave negative results. The Mantoux reaction was positive with a 1:100,000 dilution of tuberculin. Roentgen examination of the leg showed no involvement of the bone.

The patient has received a few injections of a bismuth and of a mercury preparation. A number of the ulcerations have healed in the course of this treatment, but at the same time new ulcerations are forming along the border. Biopsy showed a definite tuberculous structure.

FAVUS. Presented by DR. GEORGE M. LEWIS.

S. B., a girl aged 6 years, from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, acquired an infection of the scalp three years ago. When she was examined four months ago there were a few scattered areas of crusting with a moderate degree of alopecia; no scarring was apparent. Examination under filtered ultraviolet rays gave positive results. Infected hairs were observed in a potassium hydroxide preparation, and Achorion Schoenleinii was grown in culture. A trichophytin test was negative. Since the infection was fairly localized and there was no evidence of further spreading, treatment by manual depilation was begun. An ointment containing salicylic acid and sulfur has been applied. For the past two months no infected hairs have been observed.

DISSEMINATED LUPUS VULGARIS. Presented by DR. OSCAR L. LEVIN and DR. S. H. SILVERS.

L. B., a woman aged 22, single, a stenographer, states that she has had involvement of the chest since she was aged 7 years, at which time she had pleurisy with effusion on the right side. She had pneumonia several times and had chorea at 7 and at 12 years of age. Seven years ago she underwent an operation for a destructive lesion of the right shoulder. Three years ago, a positive diagnosis of pulmonary tuberculosis was established, being based on positive results of examination of the sputum and on evidence obtained by roentgen and by physical examination. The patient has spent most of the past three years in various institutions for the treatment of tuberculosis. She has two sisters who also suffer from pulmonary tuberculosis.

The cutaneous lesions appeared for the first time six years ago, being scattered in isolated fashion. Some of them were cauterized, but new lesions immediately reappeared in the scars as well as in new distant areas.

The present status is as follows: 1. The chest shows areas of localized pneumothorax in the basal and axillary portions on the left side. These areas are filled with fluid. There are thickened pleura on the left side, retraction of the left portion of the chest with mediastinal shift and proliferative changes in the apex of the right lung.

2. Roentgen examination of the osseous system showed a destructive lesion of the head, neck and adjacent portion of the shaft of the humerus. The glenoid fossa was irregular and jagged.

3. The latest examination of the sputum showed no tubercle bacilli. Analysis of the gastric content, chemical examination of the blood, the Wassermann, the Kahn test and urinalysis gave negative results. The blood contained 4,300,000 red cells, 80 per cent hemoglobin, and 5,300 white cells. The differential count showed 69 per cent polymorphonuclears. A test with a 1: 10,000,000 dilution of tuberculin was positive.

4. Scattered over the body are numerous yellowish red, shiny or slightly scaly papules and nodules from the size of a pinhead to that of a grape seed. Some are more resistant to the palpating finger than others. On the upper portion of the shoulder region there is an irregular dollar-sized scar, the periphery of which is ringed with a typical papulonodular lesion. Some lesions also appear in the region of the scar. Similar but smaller lesions are present on the forehead, arms, neck, ear and thigh. In one or two areas, such as the extensor surface of the right arm, a flat pigmented atrophic scar about the size of a 5 cent piece is seen.

The therapy which proved most helpful while this patient was under our care for the past eleven months was administration of massive doses of ultraviolet radiation, of large doses of cod liver oil and of a high caloric diet with an abundance of calcium, and rest, both mental and physical. The patient gained 40 pounds (18.1 Kg.). The lesions are much flatter, and no new ones have appeared. The condition of the lungs also has showed gradual and definite improvement.

DARIER'S DISEASE. Presented by DR. B. LAPOWSKI and DR. ABRAHAM WALZER.

A. Z., a girl aged 16, is presented from the Good Samaritan Dispensary and Hospital because of an eruption of seven years' duration involving the temporal region, nasolabial folds, neck, upper portion of the chest anteriorly and posteriorly, upper portion of the abdomen and pubic region. The patient is one of five children. She has never been ill. There is no history of any cutaneous disease in the family. When the patient was 9 years old an eruption appeared on both shoulders and disappeared. Five years after this, "patches" appeared on the scalp; these have persisted. About a year and a half ago lesions again appeared on the shoulder and spread to the present locations.

There are pinpoint lesions with adherent soft scabs, which increase in size and form papules from the size of a pinhead to that of a millet seed; these papules are surmounted by a brownish or grayish adherent dirty-looking scab and show faint surrounding erythema. When these scabs are removed no bleeding occurs. In instances in which the lesions have coalesced to form small patches the individual lesions can still be seen. The nails show either elongated striations or are ragged and broken along the free border. The scalp shows seborrhea-like patches. The palms show keratotic follicular points. The mucous membranes of the mouth show no lesions, but there is a scrotal tongue. The patient complains of very little itching.

Biopsy showed typical Darier's disease.

Book Reviews

Cosmetic Dermatology. By Herman Goodman. Cloth. Price, $6.50. Pp. 591. New York: McGraw-Hill Book Company, 1936.

This book contains a great deal of useful information. It is divided into two parts. One part is a dictionary of names of ingredients, representing a full pharmacopeia of substances used in making cosmetics and employed in the treatment of diseases of the skin. Both official and unofficial preparations are listed; the names are arranged alphabetically, and there is a cross-index. The formula, the source of the drug, its physical and chemical properties and its action and purpose in "dermato-cosmetics" are given. This part of the book is a useful section of about 190 pages.

The second part is entitled "Practical Cosmetic Dermatology and Tested Formulary." There is no question as to the value of a tested formulary. Formulas for all sorts of cosmetics are given, and it is claimed that they have all been tested and found both workable and useful. The worth of such a section in a book is apparent. But the author's attempt to correlate all of this valuable information with practical dermatology was not accomplished as well as it might have been. One cannot tell whether this section is written for the physician or for the cosmetician; there is too much information for the latter and an insufficient amount if for the former. The author "hesitates to more than mention the malignant changes which are obviously beyond the domain of cosmetics," yet there are discussions of psoriasis, poison ivy dermatitis, fungous infections, scabies and, believe it or not, pediculosis pubis. On page 324 there is an unmistakable implication that the topical use of thallium acetate creams for superfluous hairs is valuable. Again, the author makes the statement that pores cannot be clogged by applications of cold-cream. These observations, of course, are not in accord with the experiences of most observers. The chapter on eczema begins with the sentence "Dermatitis is not taken literally. Inflammation of the derma covers a multitude of errors." The reviewer ventures the opinion that if the author should ever suffer from dermatitis produced by a multitude of errors (occasionally even at the hands of cosmeticians) he will take it seriously and literally. Meaningless statements of this sort occur too frequently; occasionally there is an iconoclasm, and altogether the part of the work dealing with practical cosmetic dermatology, which apparently was meant to be the main portion of the book, is poorly presented, poorly written and of little real practical value. The other sections do give the book some value as a source of information.

Primer Censo Quinquenal Reglamentario de la Lepra en la Republica Mexicana, 1930-1934. Departmento de Salubridad Publica, Servicio de Profilaxis de la Lepra.

An elaborate census of leprosy in the republic of Mexico has just been published by the Federal Department of Health under the leadership of Dr. Jesus Gonzáles Urueña. It is embodied in a 136 page book containing many charts and maps and is similar to the recent census of mal del pinto which was conducted under the same auspices.

The census of leprosy was taken during the five year period from 1930 to 1934 inclusive. It shows that the disease exists in every one of the thirty-one states, though in each of four of them only a single case was reported. The highest incidence was observed in the federal district, 451 cases being reported from that district.

The census showed a total of 2,449 lepers, of whom nearly three fifths were males. No patient under 5 years of age was observed, and there were only 72 over 70. The greatest incidence of the disease was noted in the third decade.

By far the largest number of patients were of mixed blood, the incidence in that group being 1,692, whereas only 374 were white persons and 371 full-blooded Indians. Attention is called to the low incidence of the disease in full-blooded Indians, who form the greater part of the population. The social and economic position and mode of living were poor in the great majority of cases, as might have been expected.

Four types of leprosy are described—macular, neural, tubercular and mixed. There were 479 cases each of the macular and of the neural type, 757 cases of the tubercular type and 734 cases of the mixed type.

In a little less than one fifth of the cases there was a familial history of leprosy, according to information given by the patients. About three fifths of the patients had open lesions. Of the total number of lepers, 375 were hospitalized and 403 were rigidly isolated at home. A little more than half of the patients had received treatment.

By-Effects in Salvarsan Therapy and Their Prevention, with Special Reference to the Liver Function. By V. Genner. Translation from the Danish by Hans Anderson, M.D. Pp. 360. Copenhagen: Levin and Munksgaard, 1936.

The author has correlated the complications of treatment of syphilis as observed in the patients of the Rigshospital, Copenhagen, Denmark. The material is presented in three parts: The first section consists of data on arsphenamine erythema, jaundice, albuminuria and involvement of the joints. The second section deals with the by-effects of arsphenamine and the value of a dextrose solution as a solvent in the prevention of such complications. The value of "functional liver tests" in the appraisal of these complications is likewise discussed. The third section is based on the "functional liver tests" made on a group of hospitalized patients. The last eighty pages of the book consist of 125 case reports.

The observations and deductions presented by the author are in accord with the experiences reported by numerous syphilologists in the American medical literature in the past. In this country the test of hepatic function has not received as much credit as is accorded it by Genner. The author in a résumé conveys the general tenor of the book when he writes that ". . . it is practical by watching for the subjective by-effects and employing the functional liver tests to differentiate those patients who are intolerant to salvarsan and to plan for them a suitable individualized treatment, so that they too may go through the salvarsan therapy without serious or permanent injury."

The material in the book is well presented; the translation into English is exceptionally well done; the references are not too numerous, especially on controversial points; all told, the book is an excellent résumé of some of the more common complications of arsphenamine therapy, and it is recommended to those interested in this field of medicine.

Medical Classics [A periodical]. Compiled by Emerson Crosby Kelly. Volume I, Number 1. Baltimore: Williams and Wilkins Company, September, 1936.

This exceedingly meritorious undertaking to republish medical classics not simply because of their historical value but because of their interest to contemporary physicians should be encouraged. This number is of particular interest to dermatologists because it is devoted to Sir James Paget and because it contains his original paper on disease of the nipple and his papers on osteitis deformans.

Dermatologists who have not read it should read Paget's description of his disease of the nipple in order to see how completely a disease can be described from a study of its clinical manifestations alone. Indeed, Paget's style makes the whole volume worthy of reading. His descriptions can be studied with benefit.

This new periodical, each volume of which will consist of ten numbers, will reproduce many classic descriptions of diseases. It is the sort of publication which every physician needs in his library.

Histological Technique. By Aram A. Kragian. Pp. 217, with 5 illustrations. Los Angeles: Published by the author, 1936.

This book on laboratory technic is written by a man who is intensely interested and has had a vast experience in that subject. The author began his training under Prof. W. G. MacCallum of the Johns Hopkins Hospital and has been for many years a technician in a pathologic laboratory. He writes with clarity and with extraordinary fulness of knowledge of practical laboratory methods. The book deserves a welcome among those who must know the innumerable details

Books Received

TISSUE IMMUNITY. Reuben L. Kahn, University of Michigan. Pp. 707, with 6 illustrations and 2 colored plates. Springfield, Ill.: Charles C. Thomas, Publisher, 1936.

PRAKTISCHE THERAPIE DER HAUTKRANKHEITEN. Dr. Karl Steiner. Price, 4.80 marks. Pp. 116. Berlin: Julius Springer, 1937.

FÖRHANDLINGAR VID NORDISK DERMATOLOGISK FÖRENINGS. Harald Boas and Svend Emanuel. Pp. 607. Helsingfors: Mercators Tryckeri, 1936.

News and Comment

DEATHS

Dr. George Henry Fox, of New York, died on Monday, May 3, in his ninety-first year.

CORRECTION

A patient suffering from granuloma inguinale was presented by Dr. M. E. Ebert at the March 18, 1936, meeting of the Chicago Dermatological Society. In the report of the proceedings of the society, published in the February issue of the ARCHIVES (**35**:325, 1937), however, the title (page 335) was incorrectly given as "Lymphogranuloma Venereum."

Directory of Dermatologic Societies *

INTERNATIONAL

Ninth International Congress of Dermatology and Syphilology

American Secretary: Dr. Howard Fox, 140 E. 54th St., New York.

FOREIGN

British Association of Dermatology and Syphilology (Canadian Branch)

J. J. McGovern, President, 4005 Dorchester St., Montreal.
F. L. Boulais, Secretary-Treasurer, 2061 St. Denis St., Montreal.
Place: Montreal. Time: May 1937.

Royal Society of Medicine, Section of Dermatology

H. W. Barber, President, 7, Devonshire Pl., London, W. 1.
Louis Forman, Secretary, 7, Devonshire Pl., London, W. 1.

NATIONAL DERMATOLOGIC SOCIETIES

American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

Paul A. O'Leary, Chairman, 102 Second Ave., S.W., Rochester, Minn.
J. Bedford Shelmire, Secretary, 1719 Pacific Ave., Dallas, Texas.
Place: Atlantic City, N. J. Time: June 7-11, 1937.

American Board of Dermatology and Syphilology

Howard Fox, President, 140 E. 54th St., New York.
C. Guy Lane, Secretary, 416 Marlborough St., Boston.

American Dermatological Association

John H. Stokes, President, 3800 Chestnut St., Philadelphia.
F. D. Weidman, Secretary, University of Pennsylvania, Philadelphia.
Place: Sky Top, Pa. Time: June 3-5, 1937.

SECTIONAL DERMATOLOGIC SOCIETIES

Central States Dermatological Association

Samuel Goldblatt, President, 3208 Colerain Ave., Cincinnati.
Raymond G. Senour, Secretary-Treasurer, 19 W. 7th St., Cincinnati.
Place: Cleveland. Time: Dec. 5, 1936.

Mississippi Valley Dermatological Society

A. H. Conrad, President, 3720 Washington Blvd., St. Louis.
Roy L. Kile, Secretary-Treasurer, 3720 Washington Blvd., St. Louis.

Northern New Jersey Dermatological Society

Henry J. F. Wallhauser, President, Medical Tower, Newark.
Louis J. B. LeBel, Secretary, 165 Grant Ave., Nutley.
Place: Academy of Medicine of Northern New Jersey, Newark. Time: Third Tuesday of January, March, May, September and November.

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*Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Harry M. Robinson, Chairman, 106 E. Chase St., Baltimore, Md.
Winston U. Rutledge, Secretary, 332 W. Broadway, Louisville, Ky.
Place: New Orleans. Time: Nov. 30-Dec. 1-3, 1937.

STATE DERMATOLOGIC SOCIETIES

CALIFORNIA MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, DERMATOLOGY AND SYPHILOLOGY SECTION

Thomas J. Clark, Chairman, 400, 29th St., Oakland.
George V. Kulchar, Secretary, 450 Sutter St., San Francisco.

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON DERMATOLOGY

Maurice J. Strauss, Chairman, 41 Trumbull St., New Haven, Conn.
Edward A. Abbey, Secretary, 442 Temple St., New York.

FLORIDA SOCIETY OF DERMATOLOGY AND SYPHILOLOGY

J. L. Kirby-Smith, Chairman, 204 Laura St., Jacksonville.
W. M. Sams, Secretary, 310 Ingram Bldg., Miami.

LOUISIANA DERMATOLOGICAL SOCIETY

M. T. Van Studdiford, President, 912 Pere Marquette Bldg., New Orleans.
R. A. Oriol, Secretary-Treasurer, Maison Blanche Bldg., New Orleans.

MASSACHUSETTS MEDICAL SOCIETY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Harvey P. Towle, President, 453 Marlborough St., Boston.
Rudolf Jacoby, Secretary, 270 Commonwealth Ave., Boston.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Albert R. McFarland, Chairman, 227 Alexander St., Rochester.
Harry C. Saunders, Secretary, 161 W. 87th St., New York.
Place: Rochester. Time: May 25-26, 1937.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA SECTION ON DERMATOLOGY

Abraham Strauss, Chairman, Medical Arts Bldg., Philadelphia.
L. G. Bembauer, Secretary, 5026 Jenkins Arcade Bldg., Pittsburgh.

MICHIGAN STATE MEDICAL SOCIETY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

G. Warren Hyde, Chairman, 2501 W. Grand Blvd., Detroit.
Ruth Herrick, Secretary, 26 Sheldon Ave., Grand Rapids.

MINNESOTA DERMATOLOGICAL SOCIETY

John Madden, President, 350 St. Peter St., St. Paul.
F. W. Lynch, Secretary-Treasurer, Lowry Medical Arts Bldg., St. Paul.
Time: First Friday in October, December, February and April.

OKLAHOMA STATE DERMATOLOGICAL SOCIETY

Charles P. Bondurant, President, 412 Medical Arts Bldg., Oklahoma City.
Darrell G. Duncan, Secretary, 914 Medical Arts Bldg., Oklahoma City.

TEXAS DERMATOLOGICAL SOCIETY

C. M. Griswold, President, 1215 Walker Ave., Houston.
Everett R. Seale, Secretary, 1215 Walker Ave., Houston.

LOCAL DERMATOLOGIC SOCIETIES

Baltimore-Washington Dermatological Society

Leon Ginsburg, President, The Walbert, Baltimore.
Francis A. Ellis, Secretary, 104 W. Madison St., Baltimore.

Bronx Dermatological Society

Paul Gross, Chairman, 35 E. 84th St., New York.
Henry Silver, Secretary, 290 West End Ave., New York.

Brooklyn Dermatological Society

George F. Price, President, 884 Lincoln Pl., Brooklyn.
Mortimer J. Cantor, Secretary, 907 St. Marks Ave., Brooklyn.
Time: Third Monday of each month except June, July, August and September.

Buffalo-Rochester Dermatological Society

I. J. Arnsson, President, 468 Delaware Ave., Buffalo.
Richard L. Saunders, Secretary, 333 Linwood Ave., Buffalo.

Central New York Dermatological Society

George M. Fisher, President, 264 Genesee St., Utica.
Rudolph Ruedemann Jr., Secretary-Treasurer, 214 State St., Albany.

Chicago Dermatological Society

Otto H. Foerster, President, 208 N. Wisconsin Ave., Milwaukee.
Herbert Rattner, Secretary, 7 W. Madison St., Chicago.

Cincinnati Dermatological Society

Raymond G. Senour, President, Carew Tower, Cincinnati.
Leon Goldman, Secretary-Treasurer, Doctors Bldg., Cincinnati.

Cleveland Dermatological Society

John E. Rauschkolb, President, 1705 Medical Arts Bldg., Cleveland.
C. L. Cummer, Secretary, 1010 Hanna Bldg., Cleveland.

Detroit Dermatological Society

W. G. Wander, President, 509 Kresge Bldg., Detroit.
G. Warren Hyde, Secretary-Treasurer, 2501 W. Grand Blvd., Detroit.

Los Angeles Dermatological Society

Harry P. Jacobson, Chairman, 2007 Wilshire Blvd., Los Angeles.
Thomas W. Nisbet, Secretary, 65 N. Madison Ave., Pasadena, Calif.
Time: Second Tuesday of each month, October to May, inclusive.

Manhattan Dermatologic Society

Isidore Rosen, Chairman, 106 E. 54th St., New York.
Mihran B. Parounagian, Secretary, 126 E. 39th St., New York.

Montreal Dermatological Society

B. Usher, President, 1538 Sherbrooke St., W., Montreal, Canada.
Paul Poirier, Secretary, 450 Sherbrooke St., E., Montreal, Canada.

New England Dermatological Society

William P. Boardman, President, 388 Marlborough St., Boston.
J. Harper Blaisdell, Secretary, 45 Bay State Road, Boston.

New York Academy of Medicine, Section of Dermatology and Syphilis

J. Gardner Hopkins, Chairman, 102 E. 78th St., New York.
David Bloom, Secretary, 135 E. 50th St., New York.

New York Dermatological Society

Paul E. Bechet, Chairman, 55 Park Ave., New York.
Eugene F. Traub, Secretary, 140 E. 54th St., New York.

Omaha Dermatological Society

J. A. Borghoff, Chairman, 1319 Medical Arts Bldg., Omaha.
Donald J. Wilson, Secretary, 1113 Medical Arts Bldg., Omaha.

Philadelphia Dermatological Society

Vaughn C. Garner, Chairman, Germantown Professional Bldg., Philadelphia.
Thomas Butterworth, Secretary, 238 N. 5th St., Reading, Pa.

Pittsburgh Dermatological Society

Joseph J. Hecht, President, 506 Medical Arts Bldg., Pittsburgh.
Abraham Fisher, Secretary, 530½ Fifth Ave., McKeesport, Pa.

St. Louis Dermatological Society

A. H. Conrad, President, 3720 Washington Blvd., St. Louis.
Roy L. Kile, Secretary-Treasurer, 3720 Washington Blvd., St. Louis.
Place: Barnard Free Skin and Cancer Hospital. Time: Second Wednesday of each month.

San Francisco Dermatological Society

L. R. Taussig, President, 384 Post St., San Francisco.
John M. Graves, Secretary, 909 Hyde St., San Francisco.